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Article

Effect of dapagliflozin and atorvastatin on the kidney of type 2 diabetic rat model

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Abstract

Background: Diabetic dyslipidemia is a significant contributor in the pathogenesis of type 2 diabetes (T2D). Dapagliflozin and atorvastatin are important lines in treatment of T2D in patients with cardiovascular diseases. The present study compared the effect of dapagliflozin and atorvastatin alone or their combination on lipids and their vascular impact in T2D rats.
Methods: 40 male albino rats were included in the study and divided into 2 main groups. Group A (8 rats) which served as normal control. Group B (32 rats) were streptozotocin - nicotinamide-induced diabetic rats. Subgroups (B-1, B-2, B-3 and B-4) received (no medications, dapagliflozin, atorvastatin and dapagliflozin+ atorvastatin) respectively. Urine albumin/creatinine ratio (UACR), glycosylated hemoglobin (HbA1c%), fasting serum glucose (FSG), serum low density lipoprotein (LDL-C), serum high density lipoprotein (HDL-C), serum triglycerides (TGs), serum lipoprotein(a) Lp (a), highly sensitive C-reactive protein (hs-CRP) and advanced glycation end products (AGEs), were assessed. Qualitative and quantitative histological examination of kidneys focused on renal corpuscles. Means of mesangial expansion were also determined.
Results: Dapagliflozin group showed a significant decrease in levels of FSG, HbA1C%, TGs with a significant increase in HDL-C level & insignificant increase in both LDL-C and Lp (a)& insignificant decrease in AGEs and hs-CRP & significant increase in UACR. Atorvastatin group resulted in insignificant increase in levels of FSG, HbA1C% & significant decrease in levels of LDL-C, Lp (a),TGs, AGEs and hs-CRP &UACR with a significant increase in HDL-C level. Combination group significantly improved all studied parameters. Histologically; dapagliflozin

depicted nephrotoxic effect with complete obliteration of most of the urinary spaces. Atorvastatin revealed therapeutic effect with less renal affection. Combination group ameliorated nephrotoxic effect of dapagliflozin and improved its mesangial expansion values. There were positive correlations between LDL-C & hs-CRP, AGEs and mesangial expansion.
Conclusion: Combination of atorvastatin with dapagliflozin can ameliorate its possible nephrotoxic effect.

Keywords: Diabetic dyslipidemia, Vascular impact, Dapagliflozin.

Introduction

Diabetes mellitus (DM) has emerged as a serious public health problem in this century with an increasing prevalence along the past few decades in different parts of the world and future estimates are even more alarming (1). Diabetic kidney disease (DKD) is a frequent microvascular complication of DM, affecting nearly 25% of the diabetic population. Moreover, it is considered a principal cause of end-stage renal disease (ESRD) (2).

The main possible culprit of these vascular complications is the state of insulin resistance and chronic hyperglycaemia in T2D. It may be a common basis of multiple pathogenic events occurring together in the pathogenesis of diabetic complications.These events can be described through three broad categories: diabetic dyslipidemia, chronic low-grade inflammation and advanced glycation end products (3). Diabetic dyslipidemia, consists of triad of plasma lipid alterations of DM, including hypertriglyceridemia, low HDL-cholesterol levels and high small dense LDL-cholesterol (sd LDL-C) levels. This triad is a significant contributor to accelerated atherosclerosis in DM and other insulin-resistant conditions (4). Moreover, it has been reported that lipoprotein (a) [Lp (a)] levels were elevated in patients with T2D (5). Lipoprotein (a) is a modified LDL particle that is considered an important risk factor for cardiovascular diseases (CVD) in diabetic patients via its proatherogenic, prothrombotic and inflammatory properties (6).

Importantly, diabetic dyslipidemia far overweighs all other pathogenic pathways, hence it is essential to emphasize that the pharmacologic therapies do not aggravate the associated lipid abnormalities and preferably leads to their improvement (7).

Dapagliflozin is one of sodium-glucose co-transporter-2 (SGLT2) inhibitors that are marking a new era in the treatment of T2D due to showing significant mortality improvement in patients with CVD (8).

Atorvastatin is a potent active inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme in de-novo cholesterol synthesis (9). The usage of statins in diabetics has long term benefits through decreasing morbidity, mortality and preventing cardiovascular events (10).

The current study was conducted with the objective to compare the effect of dapagliflozin and atorvastatin alone or their combination on serum lipid profile and their vascular impact in type-2 diabetic rats.

Methods

Experimental design

The experiment was performed according to the guidelines of Laboratory Animal Care and Ethical Committee (Faculty of Medicine, Alexandria University), based on international regulations of animal care (IRB No.: 00007555-FWA No.: 00018699).

The current study was conducted on 40 male albino rats of body weight ranging from 150-200 g. Initially, animals were randomly divided into **2 main groups**: **Figure (1)**

I. **Group A: (normal control group)** (8rats) Animals in this group were fed normal rat chow throughout the study. They received a single 1ml intraperitoneal (i.p.) injection of 0.1 molar citrate buffer at the beginning of the study, followed by administration of 2.0 ml of gum acacia (2%) orally daily for 8 weeks.
II. **Group B: (Type 2 Diabetic group) (STZ-NA-induced diabetic rats)** (32 rats)

Induction of DM: A single dose of 65 mg/kg streptozotocin (STZ) was freshly prepared in 0.1 M citrate buffer and injected intraperitoneally (i.p.) to induce T2D after15 min of nicotinamide (NA) injection (230 mg/kg, i.p.). Nicotinamide was prepared in normal saline. The Molar solution was prepared as 1.47 g of sodium citrate dissolved in 50 mL of distilled water. Then with the help of citric acid, the pH of the solution was adjusted to 4.5, as measured by the pH meter (11, 12).

This model, as a model for non-obese T2D, has been reported to be more appropriate for both biochemical and pharmacological researches which assess the potential antidiabetic effects of pharmacological and natural agents on the course of vascular diabetic complications (13).

Induction of diabetes of this group was confirmed after 72 hours by fasting blood glucose (FBG) ≥ 250 mg/dl. Finally, diabetic animals were further subdivided into 4 groups each of 8 rats:

- **Group B-1 (diabetic control group):** Animals received 2.0 ml of 2% gum acacia orally daily.
- **Group B-2 (Dapagliflozin-treated diabetic group):** Animals received dapagliflozin (1 mg/kg) suspended in 2.0 mL of gum acacia (2%) orally daily (14).
- **Group B-3 (Atorvastatin-treated diabetic group):** Animals received atorvastatin (10 mg/kg) in the same suspension orally daily (15).
- **Group B-4 (Dapagliflozin + atorvastatin-treated diabetic group):** Animals received dapagliflozin & atorvastatin as previously mentioned in B-2 and B-3.

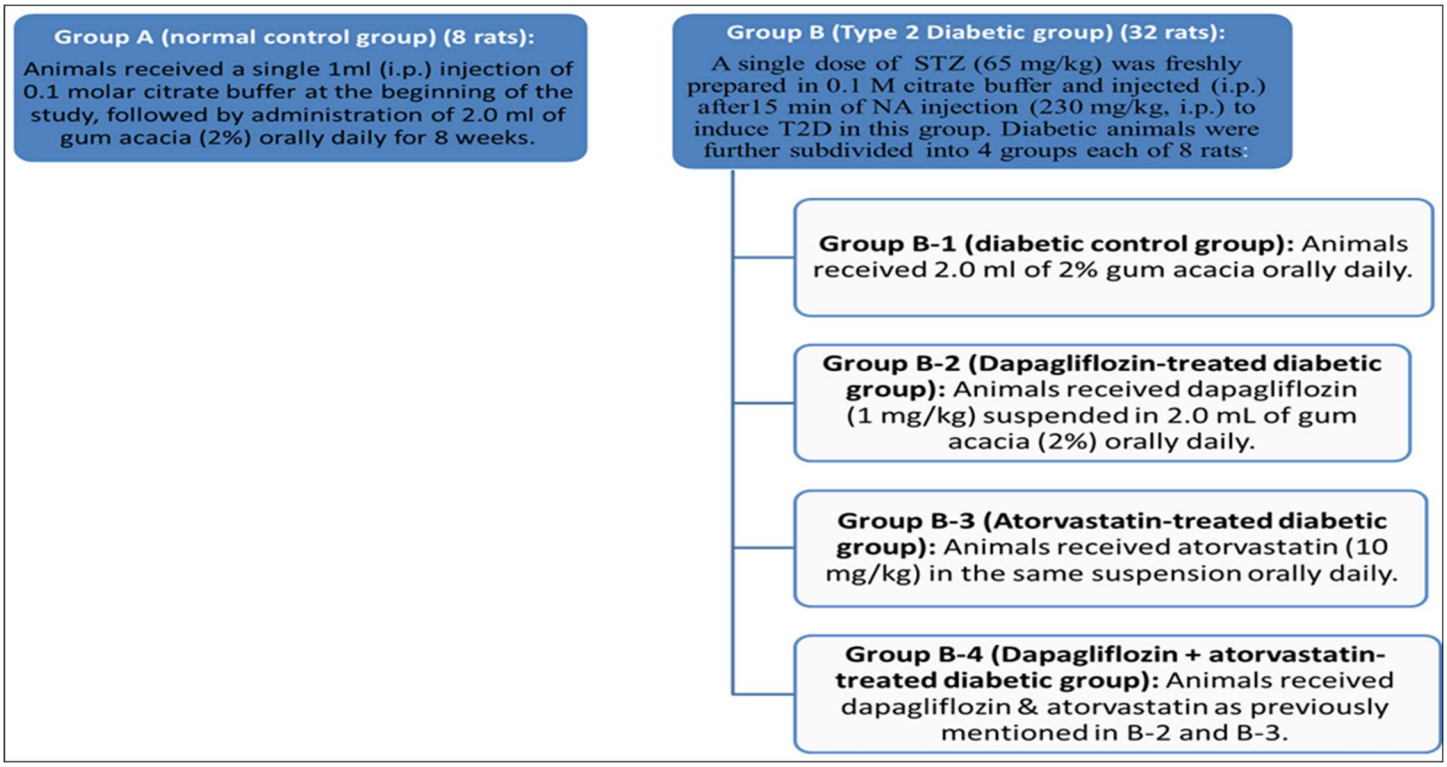

Figure (1): Schematic diagram showing the experimental conditions of each group. (STZ): Streptozotocin / (NA): Nicotinamide.

I). Biochemical analysis

After the study period (eight weeks), the following samples were collected:

1. **Urine samples:** 24 hours before sacrification, each rat was kept in a special metabolic cage with perforated platform to collect the urine output starting from 8 a.m. to 8 a.m. next day (16). The following parameter was assessed: (Urine albumin/creatinine ratio (UACR) by colorimetric method)
2. **Blood samples:** (after fasting for 12 hrs)

Under ketamine anesthesia, blood samples were collected from the abdominal aorta for the assessment of following parameters:

1.Glycosylated hemoglobin (HbA1C) & Fasting serum glucose (FSG) by colorimetric method.

2.Lipid profile (serum LDL-C, HDL-C and TGs) by colorimetric method.

3.Serum Lp (a) by ELISA KIT.

4.Serum highly sensitive C-reactive protein (hs-CRP) by ELISA KIT.

5.Serum advanced glycation end products (AGEs) by ELISA KIT.

6.

II). Histological analysis:

a) For histological examination, following sacrificing the rats, both kidneys were immediately removed under sterile environment. Then they were cut and fixed in buffered 10% formalin. They were processed and stained with haematoxylin and eosin (H&E) stain and then they were examined under the light microscope for histological changes. The

histological examination were focused mainly on renal corpuscles and its glomerular capillaries.

b) Quantitative Morphometric analysis of renal cortices:

Images were viewed and recorded using Olympus microscope – equipped with Spot digital camera, using computer program MATLAB software (image J, THE MATHWORKS, Inc., USA). The mean values of mesangial expansion were determined and based on the mean of pixel number.

Images were viewed and recorded using Olympus microscope – equipped with Spot digital camera, using computer program MATLAB software (image J, THE MATHWORKS, Inc., USA). The photographs of a randomly chosen section planes through renal corpuscles of each group of rats were captured at magnification 10X object lens. Ten randomly selected glomeruli of each group were measured. Thirty values for mesangial expansion (three measures in ten glomeruli) were assessed in each group. The mean values of mesangial expansion were determined and based on the mean of pixel number. Quantitative data for each group was expressed as mean ± standard deviation (SD) (17).

III). Statistical analysis

The biochemical and morphometric results were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). A parametric test; one-way analysis of variance (ANOVA) was used for comparing means between groups when the values normally distributed and a post-test Tukey's multiple comparison was used to assess the significance among groups. A value of $P < 0.05$ was considered statistically significant. All results were expressed as mean ± standard deviation (SD).

Pearson correlation test was used to assess the correlations between the lipid parameter (LDL-C) and another different studied parameter.

Diagnostic kits and reagents:

Colorimetric assay kits for glucose and glycosylated hemoglobin were purchased from (Spectrum diagnostics Co.). Colorimetric assay kit for urinary creatinine was from (Cell Biolabs.). Rat ELISA kit for albumin assay was from (Chondrex). Rat ELISA assay kits for lipoprotein (a), highly sensitive c-reactive protein and advanced glycation end products were obtained from (Bioneovan Co.). Colorimetric assay kits for LDL-C, HDL-C and TGs, were purchased from (Linear Chemicals S.L.). Streptozotocin and nicotinamide were purchased from (Sigma Aldrich Pharmaceutical co.). Citrate buffer solution and normal saline were purchased from (Arabic Laboratory Equipment Co.).

Results

I).Biochemical estimates*. Table (1)*

There was a statistically significant increase in levels of FSG, HbA1C%, LDL-C, Lp (a), TGs, AGEs and hs-CRP &UACR with a significant decrease in HDL-C level, in (B-1) as compared to (A). ($P< 0.001$)

Treatment with dapagliflozin (group B-2) showed statistically significant decrease in levels of FSG, HbA1C%, TGs with a significant increase in HDL-C level, insignificant increase in both LDL-C and Lp (a), insignificant decrease in AGEs and hs-CRP and significant increase in UACR, as compared to (B-1). ($P< 0.001$)

Treatment with atorvastatin (group B-3) resulted in statistically insignificant increase in levels of FSG, HbA1C% & significant decrease in serum levels of LDL-C, Lp (a),TGs, AGEs and hs-CRP &UACR with a significant increase in HDL-C level, when compared to (B-1). (P<0.001)

Treatment with dapagliflozin+ atorvastatin (group B-4) produced statistically significant decrease in levels of FSG, HbA1C%, LDL-C, Lp (a), TGs, AGEs and hs-CRP &UACR with a significant increase in HDL-C level, when compared to (B-1). (P< 0.001)

Table (1): Effects of 8 weeks treatment with DAPA and ATOR alone or in combinations on FSG (mg/dL), HbA1C%, lipid profile (serum LDL-C, HDL-C &TGs) (mg/dL), serum Lp (a) (ng/mL), UACR (µg/mg), serum hs-CRP (ng/mL) and serum AGEs (ng/mL) in streptozotocin-nicotinamide induced diabetic rats.

Biochemical parameters	Normal control	Diabetic control	DAPA	ATOR	DAPA + ATOR	F(P)
1. FSG (mg/dL)	84.63± 8.210	† 329.9± 34.19	†‡ 178.9± 13.68	†§ 334.2± 32.63	†‡¶ 183.5± 13.72	173.5 (<0.001*)
2. HbA1C (%)	3.788±0.2532	† 7.288± 0.8271	†‡ 5.925± 0.1389	†§ 7.850 ± 0.5952	†‡¶ 6.113±0.2295	83.51 (<0.001*)
3. Serum LDL-C (mg/dL)	34.84 ±2.982	† 93.60 ± 4.895	† 98.65± 4.411	†‡§ 59.93 ± 4.582	†‡§ 61.16± 3.613	323.4 (<0.001*)
4. Serum TGs (mg/dL)	70.88± 8.903	† 218.4±15.67	†‡ 122.4± 5.528	†‡ 109.3 ± 6.497	†‡§¶ 89.63± 7.110	292.8 (<0.001*)
5. Serum HDL-C (mg/dL)	54.55± 3.068	† 25.03± 1.591	†‡ 32.75± 3.284	†‡ 36.76± 2.660	†‡§¶ 44.88± 7.240	62.70 (<0.001*)
6. **Serum (Lp (a)) (ng/mL)**	41.20± 3.961	† 84.75± 4.464	† 87.38± 3.998	†‡§ 53.13± 3.796	†‡§ 55.38± 4.340	199.0 (<0.001*)
7. **UACR (µg/mg)**	19.50± 4.504	† 214.8± 54.61	†‡ 278.8± 62.66	†‡§ 91.50± 26.44	†‡§ 122.3± 20.50	52.04 (<0.001*)
8. **Serum hs-CRP (ng/mL)**	6.013±0.6792	† 24.75± 3.845	† 21.18± 4.119	†‡§ 16.96 ± 1.634	†‡§ 13.75± 1.282	56.87 (<0.001*)
9. **Serum AGEs (ng/mL)**	477.3± 31.97	† 922.5± 54.77	† 919.8± 52.21	†‡§ 815.0 ± 49.57	†‡§ 807.5±45.90	117.7 (<0.001*)

The data are expressed in mean ± SD. (n = number of animals in each group = 8). F, p: F and p values for ANOVA test (Sig. bet. groups was done using Post Hoc Test (Tukey)) . *: Statistically significant at p < 0.05. (FSG):fasting serum

glucose ;(HbA1c): glycosylated hemoglobin; (LDL-C) : serum low density lipoprotein-cholesterol; (HDL-C) : serum high density lipoprotein-cholesterol (TGs): serum triglycerides ;(Lp (a)):serum lipoprotein (a);(UACR): urine albumin/creatinine ratio; (AGEs): serum advanced glycation end products; (hs-CRP): serum highly sensitive C-reactive protein. **DAPA**: Dapagliflozin / **ATOR**: atorvastatin / **†:** Significant difference in comparison to normal control group, **‡:** Significant difference in comparison to diabetic control group, **§:** Significant difference in comparison to DAPA group, ¶: Significant difference in comparison to ATOR group.

II).Histological Examination: **Figure (2)**

Examination of control rat renal cortices (group A) revealed the classical appearance of renal corpuscles. **Figure (2 a)**

Examination of untreated diabetic rats' renal cortices (group B-1) revealed marked renal corpuscular affection. Different grades of expansion of glomerular tuft (mesangial expansion) were seen leading to either narrowing of urinary spaces or apparent obliteration of others. Markedly increased intracorpuscular nuclei (mesangial sclerosis) was also seen. **Figure (2 b)**

Microscopic examination of renal cortices of diabetic rats received dapagliflozin (group B-2) depicted more nephrotoxic effect with extensive corpuscular affection with severe expansion of glomerular tuft and apparently complete obliteration of most of the urinary spaces. Moreover, all the renal corpuscles showed marked increase in intracorpuscular nuclei. **Figure (2c)**

Treatment with atorvastatin (group B-3) revealed therapeutic effect with variable degree of glomerular tuft expansion, various grades of urinary spaces' obliteration and moderate increase in intracorpuscular nuclei. **Figure (2 d)**

On the other hand, combination of atorvastatin with dapagliflozin (group B-4) ameliorated the combined nephrotoxic diabetic effect and drug itself with preservation of urinary spaces in many renal corpuscles and less mesangial expansion. However few corpuscles were still depicting partial obliteration of urinary spaces with apparent increase in the density of intracorpuscular nuclei. **Figure (2 e)**

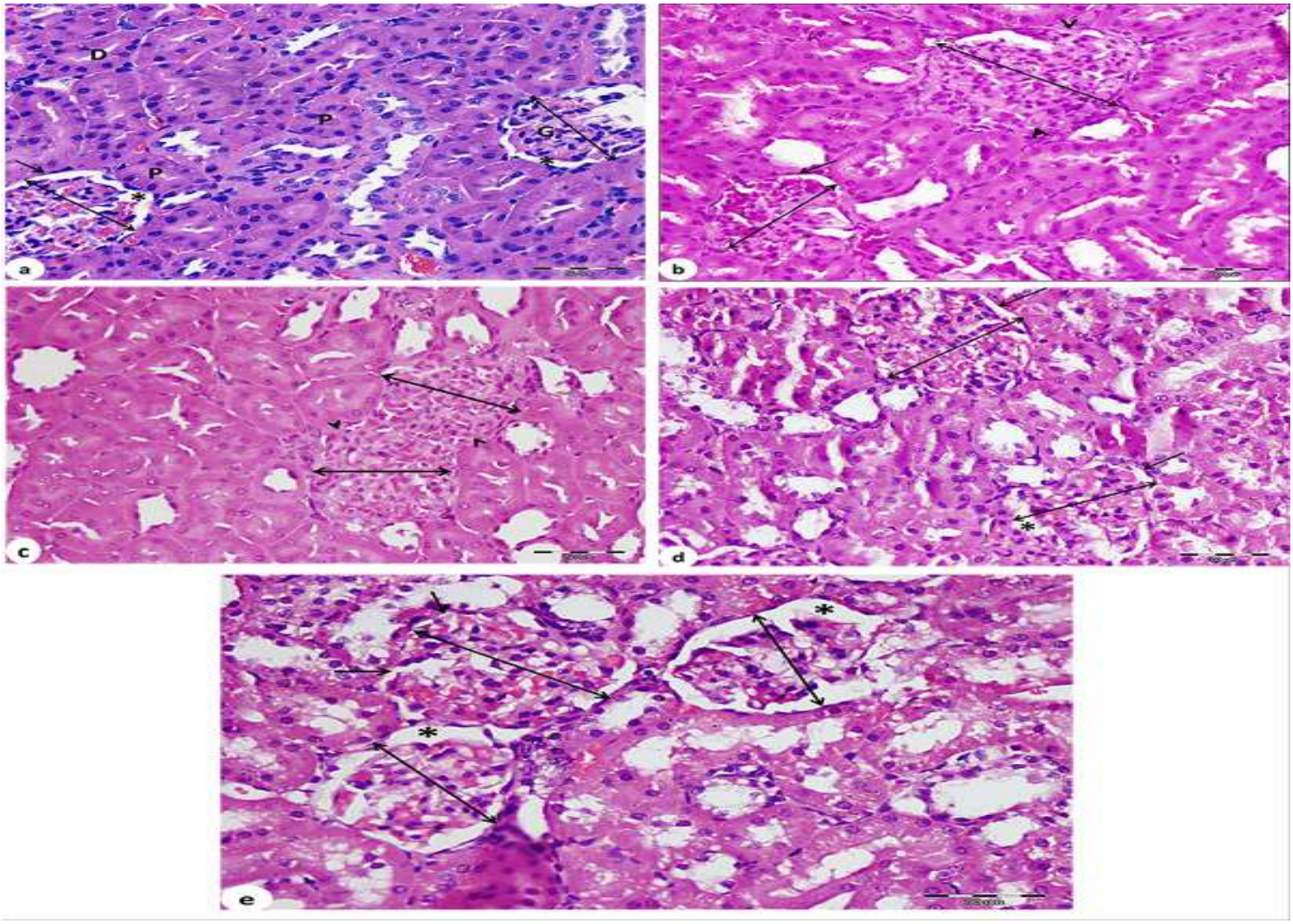

Figure (2): Renal cortices of different studied groups showing the renal corpuscles (double headed arrow) and urinary (Bowman's) spaces (*). The control group depicts classical structure showing the glomeruli (G), parietal (↑) and visceral layers of Bowman's capsule surrounded by proximal (P) and distal (D) convoluted tubules. (in a) Note the marked enlargement in the corpuscular size, obliteration of the urinary spaces and the increase in intracorpuscular nuclei in group B2 (in c), B1 (in b) respectively. Moderate histological affection was noticed in group B3 (in d) and mild affection in group B4 (in e) with apparently classical appearance of most corpuscles.

H&E stain. Mic Mag X 400 (arrow head); obliterated urinary spaces, (arrow); narrow urinary spaces and (*); preserved urinary spaces.

III). Histomorphometric results: **Table (2)**

- **Effect on the mesangial expansion (pixel)**.

There was a statistically significant increase in mean mesangial expansion levels in (B-1), as compared to (A). ($P < 0.001$)

After induction of diabetes, eight weeks treatment with dapagliflozin (group B-2) produced a statistically significant increase in mesangial expansion levels in comparison to (B-1). In contrast,

treatment with atorvastatin (group B-3) or dapagliflozin + atorvastatin (group B-4) was associated with significant decrease in mesangial expansion levels when compared to (B-1). (P< 0.001)

Table (2): Effects of 8 weeks treatment with DAPA and ATOR alone or in combination on mesangial expansion (pixel) in streptozotocin-nicotinamide induced diabetic rats.

	Normal control	Diabetic control	DAPA	ATOR	DAPA+ ATOR	F(p)
Mesangial expansion (pixel)	67.87± 12.70	† 107.9 ± 17.78	†‡ 121.6 ± 20.82	†‡§ 91.79 ±13.22	†‡§ 94.60± 20.19	40.16 (<0.001*)

The data are expressed in mean ± SD. (n = number of animals in each group = 8).

F, p: F and p values for ANOVA test (Sig. bet. groups was done using Post Hoc Test (Tukey))

*: Statistically significant at $p < 0.05$.

DAPA: Dapagliflozin / **ATOR**: atorvastatin / **†:** Significant difference in comparison to normal control group, **‡:** Significant difference in comparison to diabetic control group, **§:** Significant difference in comparison to DAPA group, ¶: Significant difference in comparison to ATOR group.

IV). Correlation results: Table (3) & Figure (3)

There was a positive correlation between (serum LDL-C) & the different studied parameters (serum hs-CRP, serum AGEs and mesangial expansion). All these correlations were statistically significant ($p < 0.001$) (n=40).

Table (3): Correlation between serum LDL-C & different studied parameters (serum hs-CRP (ng/mL), serum AGEs (ng/mL) and mesangial expansion (pixel)) in total sample (n = 40)

	Serum LDL-C	
	r	p
Serum hs-CRP	0.882	<0.001*
Serum AGEs	0.853	<0.001*
Mesangial expansion	0.752	<0.001*

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

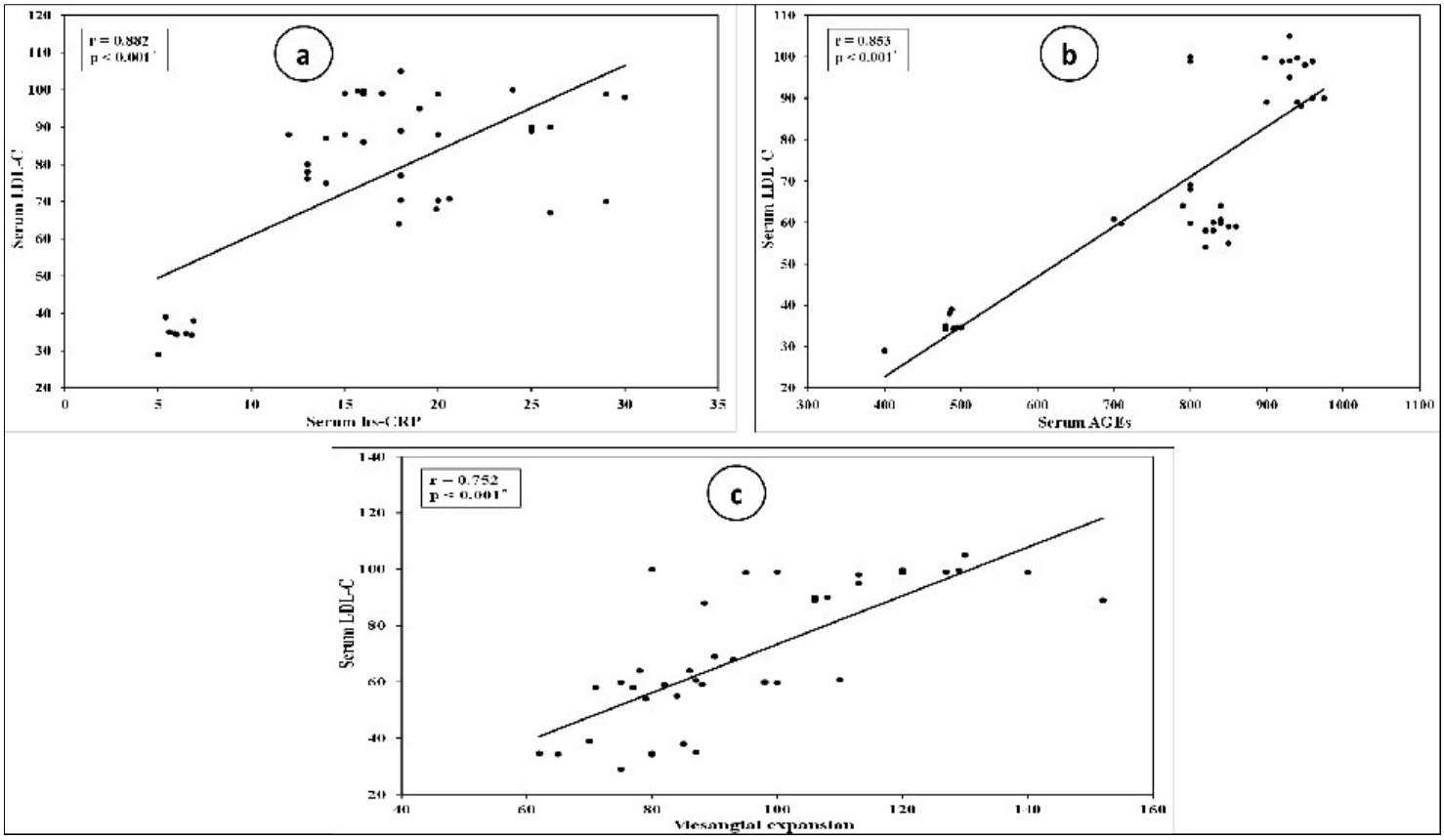

Figure (3): Correlation between serum LDL-C (mg/dL) with serum hs-CRP (ng/mL) **(a)**, serum AGEs (ng/mL) **(b)** and mesangial expansion (pixel) **(c)** in total sample (n = 40)

Discussion

It is crucial to emphasize the fact that dyslipidemia associated with DM is the major cause of morbidity and mortality because of the high rate of severe cardiovascular diseases (18). It has been considered as the most significant factor in the progress of diabetic complications by stimulating the beginning of the other pathogenic cascades. It has a key role in the activation of inflammatory pathways and release of multiple pro-inflammatory cytokines (19). It also can create an oxidative stress media that promotes the progression of glycation process in DM and augments its pathogenic effect on the vasculature (20). This was observed in our results by the presence of positive correlation between the lipid parameter (LDL-C) & (serum hs-CRP and serum AGEs).

The current study also noted a positive correlation between serum LDL-C & mesangial expansion. This can be explained by that oxidized low-density lipoprotein (Ox-LDL) particles attach to scavenger receptors in mesangial cells and podocytes, thereby elevating extracellular matrix (ECM) production as well as chemokine production, such as monocyte chemoattractant protein (MCP)-1 which stimulates monocyte migration toward the glomeruli and results in macrophage infiltration. Macrophages become foam cells via the uptake of ox-LDL and facilitate the inflammatory pathway, which all contribute to glomerular injury (21).

Dapagliflozin treated group

Eight weeks treatment of diabetic rats with dapagliflozin (group B-3) improved the studied parameters but with statistically insignificant increase in LDL-C, Lp (a) and significant increase in UACR. These results were documented by the microscopic examination of renal cortices of diabetic rats receiving dapagliflozin and by its histomorphometric results.

Although the increase in LDL-C and Lp (a) is concern, SGLT-2 inhibitors use is accompanied with reduced (CVD) risk in diabetic patients (22).

Basu et al. (23) explained the possible increased LDL-C level for SGLT-2 inhibitors by stimulating the conversion of VLDL-C to LDL-C and decrease LDL receptor-mediated LDL clearance. By reducing body weight and glucotoxicity, SGLT-2 inhibitors could attenuate insulin resistance. Enhanced insulin sensitivity elevates lipoprotein lipase (LPL) activity, which is an essential enzyme responsible for the hydrolysis of chylomicrons and VLDL leading to increased clearance of plasma TG.A decreased VLDL-triglyceride concentration leads to a decreased concentration of TG-rich acceptors.

This decreased acceptor concentration is likely to diminish the ability of cholesteryl ester transfer protein (CETP) to transfer cholesteryl ester (CE)'s from HDL to this fraction, leading to increased HDL cholesterol concentrations (24).

The effect of dapagliflozin on the kidney is matter of controversy. Some previous studies highlighted the probable pathophysiologic mechanisms of acute kidney injury (AKI) generated by SGLT-2 inhibitors following the initiation of therapy in high risk patients, such as those who are dehydrated. SGLT2 inhibition increases the excretion of glucose and sodium, leading to an osmotic diuresis, which may elevate the hazard of hyperosmolarity, dehydration, and subsequent increased risk of AKI. Glucose in the urine could also be taken up by glucose transporter (GLUT-9b) in exchange for uric acid, resulting in uricosuria that can stimulate tubular injury by crystal-dependent and crystal-independent mechanisms (25, 26).

Alternatively, Saleh et al. (27) explained the renoprotective effects of dapagliflozin through suppression of inflammation, fibrosis, endoplasmic reticulum stress, apoptosis, and by decreasing the accumulation of lipids in the kidneys. These effects might be achieved via its ability to diminish the excessive advanced glycation end products- receptor (RAGE) interaction, and consequently can inhibit the intracellular signaling cascades that lead to a plethora of proinflammatory and pro-fibrotic cellular responses via multiple downstream pathways.

Although our study revealed that dapagliflozin group had modest favorable effect on lipid profile, there was a significant elevation in UACR that was documented by nephrotoxic changes on histological examination. This could be explained by other potential mechanisms for AKI induced by dapagliflozin that exceeds its renal protective effect especially early following initiation of therapy in high risk patients. There are debates surrounding the action of SGLT2 inhibitors on renal function because the exact mechanism of SGLT2 inhibitor on kidney event is still unsettled and it might be time related. Importantly, given the protective effects of these agents on cardiovascular and long-term renal outcomes, the risk of AKI needs to be weighed against the possible benefits of SGLT2 inhibition (28).

Atorvastatin treated group

Eight weeks treatment of diabetic rats with atorvastatin (group B-3) improved the studied parameters but with statistically insignificant increase in FSG and HbA1C%. These results were reflected on the microscopic examination of renal cortices of diabetic rats receiving atorvastatin and by its histomorphometric results.

Statins have the ability to change glycemic control by lowering different metabolites such as isoprenoid and ubiquinone (CoQ10), all of which are dependent on mevalonic acid production. Isoprenoid in particular stimulates glucose uptake by GLUT-4 in adipocytes. Reduction in CoQ10 may lead to delayed ATP release in pancreatic beta cells and thereby inhibit insulin production (29).

These observations are in agreement with other studies which concluded that atorvastatin treatment could retard the progression of renal dysfunction by upgrading the renal morphologic lesions with concomitant significant lowering UACR in diabetic rats. This may be achieved by its pleiotropic effects, in addition to decreasing serum lipids, such as improving endothelial dysfunction and inhibition of inflammatory factors expression such as TNF-α, MCP-1 and IL-6 (15). Furthermore, previous data revealed that atorvastatin could lower serum AGEs levels in a cholesterol-lowering independent manner and through its anti-oxidative property. Oxidative stress mediates the production of AGEs that are by themselves a source of free radical superoxide generation as well (30).

Dapagliflozin+ atorvastatin treated group

In our study, combination of dapagliflozin with atorvastatin (group B-4) significantly improved all studied parameters. This is also translated to the histological examination of rats in this group with much more normalization of many corpuscles.

Surprisingly, our present data revealed that the good results recorded in (dapagliflozin + atorvastatin) were significant when compared to dapagliflozin group despite its renal deteriorating effect. These findings agreed with recent published report, that proved the superior protective complementary effect of dapagliflozin and atorvastatin combination therapy, as compared to monotherapy, on lipid metabolism and its associated renal oxidative stress, inflammation, fibrosis and apoptosis resulting in kidney disruption regaining in insulin resistant rat model (31).

The results of our study concluded that combination of dapagliflozin with atorvastatin could be a promising strategy to ameliorate the possible harmful renal effect of dapagliflozin.

The limitation of this study is its short duration.

Conflict of interest: None

Funding: None

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