ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Effect of Fenofibrate and Atorvastatin on Renal Functions and Histopathological changes in Experimentally-induced Diabetes in Rats.

Reham E Masoud[1]*, Mamdouh R El- Nahas[2], Azza H Zidan[3], and Naglaa H Fadel[4].

[1]Professor Of Clinical Pharmacology Faculty Of Medicine, Port Said University, Egypt.
[2]Professor Of Internal Medicine, Faculty Of Medicine, Port Said University, Egypt.
[3]Professor Of Pathology, Faculty Of Medicine, Port Said University, Egypt.
[4]Lecturer Of Internal Medicine, Faculty Of Medicine, Port Said University, Egypt.

ABSTRACT

Diabetic kidney disease (DKD) is one of the most common microvascular complications of diabetes mellitus and remains the leading cause of chronic kidney disease (CKD). This study aimed to compare the renoprotective effects of fenofibrate and atorvastatin on renal function, oxidative stress, and histopathological changes in streptozotocin (STZ)-induced diabetic nephropathy in rats. Forty adult male albino rats were randomly assigned into five groups (n = 8/group): normal control, diabetic control, diabetic rats treated with low-dose fenofibrate (30 mg/kg/day), high-dose fenofibrate (100 mg/kg/day), or atorvastatin (10 mg/kg/day). Diabetes was induced by a single intraperitoneal injection of STZ (65 mg/kg). Treatments were continued for eight weeks. Glycemic indices, blood pressure, renal function markers, urinary albumin/creatinine ratio, total cholesterol, oxidative stress biomarkers, kidney weight index, and renal histopathology were evaluated. Fenofibrate and atorvastatin significantly attenuated diabetic nephropathy through improvement of metabolic disturbances, suppression of oxidative stress, reduction of inflammation, and preservation of renal architecture. High-dose fenofibrate exhibited the greatest overall renoprotective efficacy.

Keywords: Diabetic nephropathy; Fenofibrate; Atorvastatin; Oxidative stress; Streptozotocin; Albuminuria; Histopathology.

https://doi.org/10.33887/rjpbcs/2026.17.4.1

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Diabetes mellitus (DM) is one of the fastest-growing chronic diseases worldwide and represents the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). According to the International Diabetes Federation, more than 589 million adults were living with diabetes in 2024, and this number is projected to rise substantially over the coming decades. Approximately one-third of diabetic patients eventually develop diabetic kidney disease (DKD), which markedly increases cardiovascular morbidity, mortality, and healthcare costs [1, 2].

Diabetic nephropathy is a multifactorial disorder resulting from persistent hyperglycemia, metabolic dysregulation, and intrarenal hemodynamic alterations. Chronic hyperglycemia promotes the formation of advanced glycation end products (AGEs), activation of protein kinase C, oxidative stress, inflammatory cytokines, endothelial dysfunction, and activation of the renin–angiotensin–aldosterone system (RAAS). These pathological mechanisms collectively contribute to glomerular hypertrophy, mesangial expansion, podocyte injury, basement membrane thickening, tubular degeneration, and progressive renal fibrosis [3-5].

Despite advances in glycemic and blood pressure control, many patients continue to experience progressive renal impairment, suggesting that additional pathogenic mechanisms contribute to disease progression. Increasing evidence has identified dyslipidemia as an important mediator of diabetic renal injury through lipid accumulation, oxidative stress, mitochondrial dysfunction, endothelial injury, and activation of inflammatory pathways. Consequently, lipid-modifying therapies may provide renoprotective benefits beyond their conventional lipid-lowering effects [6, 7].

Atorvastatin, a potent HMG-CoA reductase inhibitor, is widely prescribed for cardiovascular risk reduction in diabetic patients. Beyond cholesterol lowering, atorvastatin exhibits pleiotropic effects including antioxidant, anti-inflammatory, anti-apoptotic, and endothelial-protective properties, all of which may contribute to renal protection [8, 9].

Fenofibrate is a selective peroxisome proliferator-activated receptor-alpha (PPAR-α) agonist that enhances fatty acid β-oxidation, improves triglyceride metabolism, reduces lipotoxicity, and suppresses inflammatory and oxidative pathways. Experimental studies have demonstrated that fenofibrate attenuates diabetic nephropathy by reducing oxidative stress, inflammatory cytokines, macrophage infiltration, and renal fibrosis [10-12].

Although several experimental and clinical investigations have demonstrated renoprotective effects of statins and fibrates individually, direct comparative evaluation between fenofibrate and atorvastatin in experimental diabetic nephropathy remains limited. Therefore, the present study was designed to compare the effects of both agents on biochemical parameters, oxidative stress, and histopathological alterations in streptozotocin-induced diabetic nephropathy in rats.

Study design

This experimental randomized controlled animal study was conducted to evaluate and compare the renoprotective effects of fenofibrate and atorvastatin in streptozotocin (STZ)-induced diabetic nephropathy. The study was performed in accordance with the ARRIVE 2.0 guidelines for reporting animal experiments.

Experimental Animals

Forty healthy adult male albino rats weighing 170–200 g were obtained from the Animal House of the Egyptian Organization for Biological Products and Vaccines (VACSERA, Egypt). Animals were housed under standard laboratory conditions (temperature 22 ± 2°C, relative humidity 50–60%, and a 12-h light/dark cycle) with free access to standard laboratory chow and water throughout the experimental period. Animals were allowed to acclimatize for one week before initiation of the experiment.

Chemicals

Streptozotocin (STZ) was purchased from Sigma-Aldrich (St. Louis, MO, USA) and freshly dissolved in 0.1 M citrate buffer (pH 4.5) immediately before administration. Fenofibrate and atorvastatin tablets were obtained from commercially available pharmaceutical preparations and freshly suspended in distilled water before oral administration.

Induction of Experimental Diabetes

Experimental diabetes mellitus was induced by a single intraperitoneal injection of streptozotocin (65 mg/kg body weight) dissolved in freshly prepared citrate buffer (0.1 M, pH 4.5). To minimize early hypoglycemia, rats were supplied with 5% glucose solution for 24 h following STZ injection.

Seventy-two hours after STZ administration, fasting blood glucose (FBG) was measured using a glucometer. Rats with fasting blood glucose concentrations ≥250 mg/dL were considered diabetic and included in the study.

EXPERIMENTAL DESIGN

Animals were randomly allocated into five groups (n = 8 per group):

Group I (Normal Control): Healthy rats receiving distilled water orally.
Group II (Diabetic Control): STZ-induced diabetic rats receiving distilled water.
Group III (Fenofibrate Low Dose): Diabetic rats treated with fenofibrate (30 mg/kg/day, orally).
Group IV (Fenofibrate High Dose): Diabetic rats treated with fenofibrate (100 mg/kg/day, orally).
Group V (Atorvastatin): Diabetic rats treated with atorvastatin (10 mg/kg/day, orally).

Treatment was continued once daily for eight consecutive weeks.

Experimental Measurements

The following parameters were measured throughout the study:

- Fasting blood glucose (FBG)
- Body weight
- Glycated hemoglobin (HbA1c)
- Systolic blood pressure

Renal function was evaluated by measuring:

- Serum urea
- Serum creatinine
- Urinary albumin/creatinine ratio (UACR)

Lipid Profile

Total cholesterol concentrations were determined using commercially available enzymatic colorimetric kits according to the manufacturer's instructions.

Kidney Weight Index

At the end of the experimental period, both kidneys were excised, cleaned, and weighed. Kidney weight index (KWI) was calculated according to the following equation:

$$\text{Kidney Weight Index (\%)} = \text{Kidney weight (g)} / \text{Final body weight (g)} \times 100$$

Assessment of Oxidative Stress

Renal tissue homogenates were prepared for determination of oxidative stress biomarkers, including:

- Malondialdehyde (MDA)
- Glutathione peroxidase (GPx)
- Superoxide dismutase (SOD)

Measurements were performed using commercially available assay kits following the manufacturers' protocols.

Histopathological Examination

Kidney tissues were fixed in 10% neutral buffered formalin for 24–48 h, routinely processed, embedded in paraffin, sectioned at 4–5 µm thickness, and stained with hematoxylin and eosin (H&E).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics software (Version 26.0; IBM Corp., Armonk, NY, USA).

Continuous variables were expressed as mean ± standard deviation (SD). Comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc multiple comparison test.

Pearson correlation analysis was used to evaluate the relationship between histopathological injury scores and biochemical parameters.

A two-tailed P-value <0.05 was considered statistically significant.

RESULTS

Effect of Treatments on Glycemic Parameters

Baseline fasting blood glucose (FBG) levels did not differ significantly among the experimental groups ($P > 0.05$). Streptozotocin administration induced marked hyperglycemia in diabetic rats, with FBG levels remaining significantly higher than those of the normal control group throughout the experimental period ($P < 0.001$).

Treatment with fenofibrate (30 and 100 mg/kg/day) and atorvastatin (10 mg/kg/day) significantly reduced FBG levels compared with untreated diabetic rats ($P < 0.001$). The greatest reduction was observed in the high-dose fenofibrate group; however, glucose concentrations remained significantly higher than those of the normal control group (Table 1)

Table 1: Time course changes in fasting blood sugar in study groups

Group	Baseline (mg/dL)	After 1 Week	After 1 Month	After 2 Months
Control	90 ± 3	90 ± 3	90 ± 3	90 ± 3
Diabetic Control	95 ± 8	430 ± 30	420 ± 30	450 ± 35
Fenofibrate Small Dose	92 ± 5	300 ± 25*	260 ± 20*	255 ± 15*
Fenofibrate Large Dose	94 ± 5	310 ± 20*	240 ± 18*	210 ± 15*
Atorvastatin	93 ± 6	320 ± 22*	270 ± 20*	265 ± 15*

(mean ±SD) * indicate significant versus diabetic control p value <0.0001

ISSN: 0975-8585

Table 2: Comparison between HbA1c levels in study groups at the beginning of the study and after 2 months.

Group	Baseline HbA1c (%)	After 2 Months HbA1c (%)	P vs Diabetic	P vs Normal
Normal Control	4.95 ± 0.05	4.95 ± 0.05	—	—
Diabetic Control	4.00 ± 0.05	9.60 ± 0.10	—	<0.001
Fenofibrate Small Dose	4.98 ± 0.04	5.55 ± 0.10	<0.001	<0.001
Fenofibrate Large Dose	4.99 ± 0.05	5.75 ± 0.12	<0.001	<0.001
Atorvastatin	4.50 ± 0.05	5.65 ± 0.50	<0.001	<0.001

Table 3: Time course change in body weight in study groups (mean ±SD)

Group	Baseline (g)	After 1 Month (g)	After 2 Months (g)	P vs Diabetic (2 months)	P vs Normal (2 months)
Normal Control	118 ± 4	120 ± 5	141 ± 6	—	—
Diabetic Control	117 ± 5	114 ± 5	95 ± 7	—	<0.001
Fenofibrate Small Dose	116 ± 4	113 ± 6	120 ± 5	<0.05	<0.05
Fenofibrate Large Dose	118 ± 5	114 ± 6	116 ± 5	<0.05	<0.05
Atorvastatin	115 ± 8	116 ± 11	130 ± 3	<0.05	<0.05

Similarly, HbA1c levels were markedly elevated in diabetic control rats after eight weeks ($P < 0.001$). Administration of fenofibrate and atorvastatin significantly decreased HbA1c values compared with diabetic controls ($P < 0.001$), indicating partial improvement in long-term glycemic control (Table 2).

Effect on Body Weight and Blood Pressure

No significant differences in body weight or systolic blood pressure were observed among groups at baseline ($P > 0.05$).

Diabetic control animals exhibited progressive body weight loss together with a significant increase in systolic blood pressure throughout the study compared with normal controls ($P < 0.001$) table 3.

Table 4: Time course change in systolic blood pressure in study groups

Group	Baseline	After 1 Month	After 2 Months	P vs Diabetic (2 Months)	P vs Normal (2 Months)
Normal Control	104 ± 3	104 ± 3	105 ± 3	—	—
Diabetic Control	105 ± 2	120 ± 3	130 ± 3	—	<0.001
Fenofibrate Small Dose	104 ± 2	117 ± 2	110 ± 2	<0.001	<0.05
Fenofibrate Large Dose	105 ± 2	118 ± 3	112 ± 2	<0.001	<0.05
Atorvastatin	103 ± 2	112 ± 3	106 ± 4	<0.001	NS ($P > 0.05$)

Treatment with fenofibrate and atorvastatin significantly attenuated diabetes-induced weight loss and hypertension ($P < 0.05$). Atorvastatin-treated rats demonstrated the lowest systolic blood pressure among treated groups, whereas high-dose fenofibrate showed the greatest preservation of body weight table 4.

ISSN: 0975-8585

Effect on Renal Function

Serum urea and creatinine levels increased significantly in diabetic control rats compared with normal controls, indicating progressive renal dysfunction ($P < 0.001$).

Both fenofibrate and atorvastatin significantly reduced serum urea and creatinine concentrations compared with untreated diabetic animals ($P < 0.001$). Nevertheless, renal function parameters remained significantly different from those of the normal control group (Tables 5).

Table 5: Comparison of level of serum urea among study groups

Group	Baseline	After 1 Month	After 2 Months	P vs Diabetic (2 Months)	P vs Normal (2 Months)
Normal Control	12.5 ± 0.3	12.5 ± 0.3	12.7 ± 0.3	—	—
Diabetic Control	12.6 ± 0.4	29.0 ± 0.6	33.0 ± 1.0	—	<0.001
Fenofibrate Low Dose	12.6 ± 0.3	14.2 ± 0.7	14.3 ± 0.7	<0.001	<0.05
Fenofibrate High Dose	12.5 ± 0.3	15.1 ± 0.6	15.6 ± 0.6	<0.001	<0.05
Atorvastatin	12.6 ± 0.3	13.8 ± 0.3	14.1 ± 0.3	<0.001	<0.05

The urinary albumin/creatinine ratio (UACR) was markedly elevated in diabetic rats after diabetes induction ($P < 0.001$). Both drugs significantly reduced albuminuria, with high-dose fenofibrate producing the greatest improvement, followed closely by atorvastatin (Table 7).

Table 6: Serum creatinine levels over time in study groups

Group	Baseline	After 1 Week	After 1 Month	After 2 Months	P vs Diabetic (2 Months)	P vs Normal (2 Months)
Normal Control	0.70 ± 0.18	0.68 ± 0.20	0.68 ± 0.20	0.69 ± 0.18	—	—
Diabetic Control	0.72 ± 0.20	1.30 ± 0.10	2.20 ± 0.25	2.65 ± 0.30	—	<0.001
Fenofibrate Small Dose	0.72 ± 0.18	0.80 ± 0.15	1.10 ± 0.15	1.18 ± 0.12	<0.001	<0.05
Fenofibrate Large Dose	0.72 ± 0.18	1.02 ± 0.12	1.12 ± 0.15	1.05 ± 0.10	<0.001	<0.05
Atorvastatin	0.71 ± 0.18	0.78 ± 0.12	1.05 ± 0.12	0.98 ± 0.10	<0.001	<0.05

Table 7: Effect of fenofibrate and atorvastatin on urinary albumin/creatinine ratio (µg/mg) in experimental groups at different time intervals

Study groups	0 week	After 4 weeks	After 8 weeks
Normal control	29.5 ± 1.2	29.1 ± 1.4	29.8 ± 1.3
Diabetic control	28.9 ± 1.3	92.4 ± 5.6 **	118.7 ± 6.2 **
Fenofibrate (small dose)	29.1 ± 1.1	65.8 ± 3.9 *#	54.2 ± 3.1 ##
Fenofibrate (large dose)	29.7 ± 1.0	48.6 ± 2.8 ##	44.9 ± 2.4 ##
Atorvastatin-treated	28.0 ± 1.2	58.3 ± 3.5 *#	42.7 ± 2.9 ##

Values are expressed as mean ± SD (n = 8).
* $p < 0.05$, ** $p < 0.001$ vs. normal control group. $p < 0.05$, ## $p < 0.001$ vs. diabetic control group.

ISSN: 0975-8585

Effect on Total Cholesterol

Table 8: Time changes of serum total cholesterol level in study groups.

Group	Baseline (mg/dL)	After 1 Month	After 2 Months	P vs Diabetic (2 Months)	P vs Normal (2 Months)
Normal Control	95 ± 2	95 ± 3	96 ± 3	—	—
Diabetic Control	100 ± 5	220 ± 12	260 ± 15	—	<0.001
Fenofibrate Small Dose	98 ± 4	170 ± 8	150 ± 7	<0.001	<0.05
Fenofibrate Large Dose	97 ± 4	155 ± 8	130 ± 9	<0.001	<0.05
Atorvastatin	98 ± 4	165 ± 10	145 ± 8	<0.001	<0.05

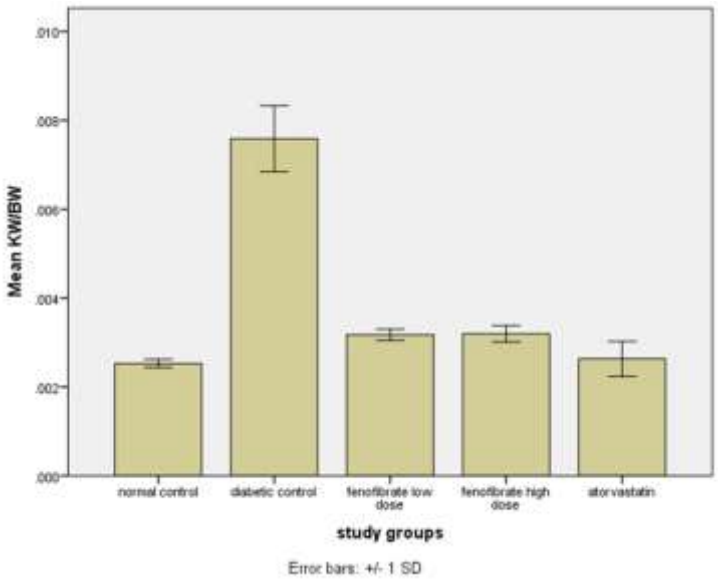
Total cholesterol levels were comparable among all groups before treatment ($P > 0.05$). Diabetes resulted in significant hypercholesterolemia compared with the normal control group ($P < 0.001$).

Administration of fenofibrate and atorvastatin significantly decreased total cholesterol levels compared with untreated diabetic rats ($P < 0.001$). High-dose fenofibrate achieved the greatest lipid-lowering effect, demonstrating a dose-dependent response (Table 8).

Effect on Kidney Weight Index

Diabetic rats developed significant renal hypertrophy, as reflected by increased kidney weight index and right kidney weight compared with normal controls ($P < 0.001$).

Treatment with fenofibrate and atorvastatin significantly attenuated renal hypertrophy ($P < 0.05$), with values approaching those observed in the normal control group (Figures 1).



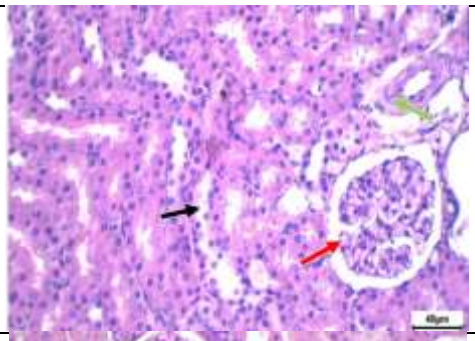
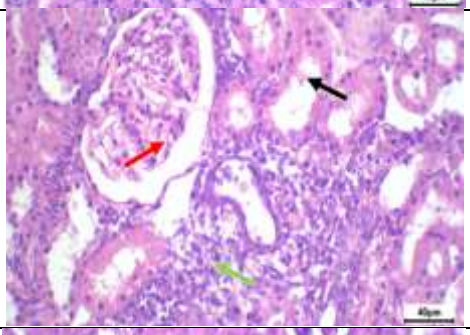
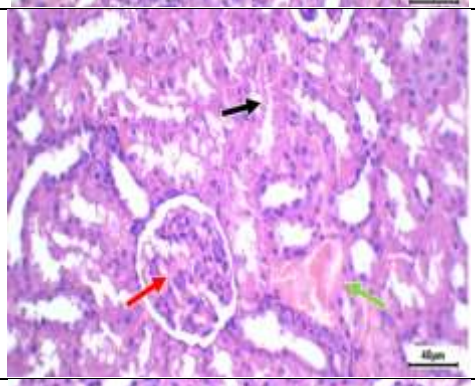
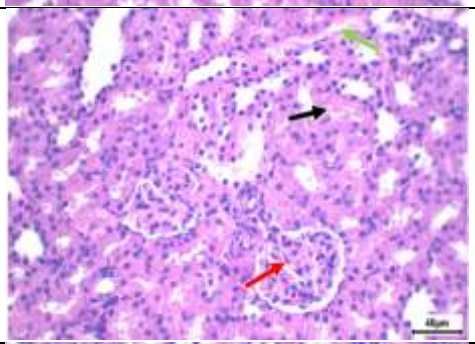
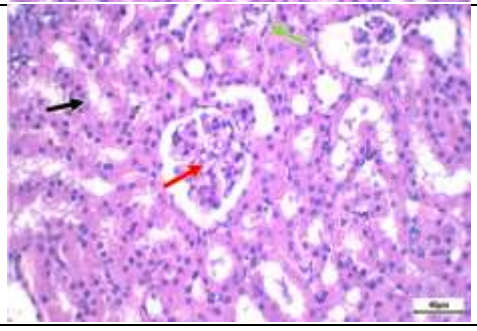
Histopathological Findings

Histopathological examination of renal tissues from normal control rats revealed preserved glomerular and tubular architecture.

In contrast, diabetic control rats exhibited marked renal injury characterized by tubular hydropic degeneration, glomerular shrinkage, increased glomerular cellularity, widening of Bowman's space, vascular congestion, and interstitial inflammatory cell infiltration.

ISSN: 0975-8585

Treatment with fenofibrate and atorvastatin markedly improved renal histology. Low-dose fenofibrate produced moderate improvement, whereas high-dose fenofibrate resulted in substantial restoration of normal renal architecture with only mild residual pathological changes. Atorvastatin also markedly improved renal histology, producing structural preservation comparable to that observed with high-dose fenofibrate (Figure 2). Study groups H&E-stained slides captured at magnification 400x.

Normal		Sections in kidney tissue showing renal cortex formed of glomeruli and tubules, glomeruli (red arrow) showed capillary tuft within thin Bowman's space and mesangial cells, tubules (black arrow) lined by columnar cells with abundant eosinophilic cytoplasm & interstitium showed thin walled blood vessels (green arow) and stroma.
Diabetic Control		Renal cortex showed moderate hydropic degeneration and vacuolation of tubular epithelial cells, glomeruli showed focal moderate increase in cellularity and focal shrinkage with degeneration and dilation of bowman's space (red arrow), stroma showed focal moderate lymphocytic infiltrate (green arrow).
Fenofibrate Small Dose		Kidney showed moderate improvement with residual moderate hydropic degeneration of tubular (black arrow) epithelial cells, glomeruli showed moderate degenerative changes (red arrow), stroma showed mild congestion (green arrow).
Fenofibrate Large Dose		Kidney showed marked improvement with residual mild changes in the form of mild focal hydropic degeneration of tubular epithelial cells (black arrow), glomeruli showed slight increase in cellularity (red arrow) and stroma showed mild congestion (green arrow).
Atorvastatin		Kidney showed marked improvement with residual mild changes in the form of mild focal hydropic degeneration of tubular epithelial cells (black arrow), glomeruli showed slight increase in cellularity (red arrow) and stroma showed unremarkable vessels (green arrow).

All Images captured using:

•Calibrated standard digital microscope camera (Tucsen® ISH100, Fuzhou, China) using Olympus® CX23 (Japan) microscope, with resolution of 10 MP (megapixels) 3656 x 2740 pixel.
•"IS Capture" software for capture and image enhancements.
UIS optical system (Universal Infinity System, Olympus®, Japan).

Oxidative Stress Biomarkers

Renal tissue from diabetic control rats showed marked oxidative stress, characterized by significantly elevated malondialdehyde (MDA) levels together with significantly reduced glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities compared with normal controls ($P < 0.001$). table 9

Table 9: Renal tissue levels of malondialdehyde (MDA), glutathione peroxidase (GPx), and superoxide dismutase (SOD) are presented as mean ± SD for the studied groups

Group	MDA	GPx	SOD	P vs Diabetic	P vs Normal
Normal Control	12 ± 1.5	48 ± 3	55 ± 3	—	—
Diabetic Control	38 ± 3	14 ± 2	18 ± 2	—	<0.001
Fenofibrate Low Dose	28 ± 2.5	26 ± 2.5	30 ± 3	<0.05	<0.05
Fenofibrate High Dose	20 ± 2	34 ± 3	40 ± 3	<0.001	<0.05
Atorvastatin	24 ± 2	30 ± 2.5	35 ± 3	<0.001	<0.05

Fenofibrate and atorvastatin significantly improved oxidative stress biomarkers compared with untreated diabetic rats ($P < 0.001$). High-dose fenofibrate demonstrated the greatest reduction in MDA levels and the highest restoration of GPx and SOD activities, indicating superior antioxidant activity among the treatment groups (Table 9).

Correlation Analysis

Pearson correlation analysis demonstrated significant positive correlations between histopathological injury scores and fasting blood glucose, HbA1c, serum urea, serum creatinine, urinary albumin/creatinine ratio, total cholesterol, and MDA levels ($P < 0.001$). Conversely, GPx and SOD activities showed significant negative correlations with renal injury scores ($P < 0.001$), indicating that reduced antioxidant defense was associated with more severe renal damage (Table 10)

Table 10: Pearson correlation coefficients between histopathological injury score and biochemical parameters in experimental groups.

Variable	Pearson Correlation (r)	P value
Fasting blood glucose	0.82	<0.001
HbA1c	0.87	<0.001
Systolic blood pressure	0.76	<0.001
Serum urea	0.91	<0.001
Serum creatinine	0.94	<0.001
Urinary albumin/creatinine ratio	0.96	<0.001
Total cholesterol	0.85	<0.001
MDA	0.92	<0.001
GPx	-0.88	<0.001
SOD	-0.90	<0.001

Values represent Pearson correlation coefficients (r). Positive values indicate direct correlations, whereas negative values indicate inverse correlations.

ISSN: 0975-8585

DISCUSSION

The present study investigated the comparative renoprotective effects of fenofibrate and atorvastatin in streptozotocin-induced diabetic nephropathy. The major findings demonstrated that experimental diabetes produced significant hyperglycemia, hypertension, dyslipidemia, renal dysfunction, oxidative stress, and severe histopathological renal injury. Treatment with both fenofibrate and atorvastatin significantly attenuated these alterations, with high-dose fenofibrate exhibiting the greatest overall renoprotective effect.

Persistent hyperglycemia is the primary initiating factor in diabetic nephropathy and promotes oxidative stress, inflammation, endothelial dysfunction, and structural renal damage. In the present study, STZ-induced diabetic rats developed marked hyperglycemia and elevated HbA1c levels, confirming successful induction of diabetes. These findings are consistent with previous reports demonstrating that STZ causes selective pancreatic β-cell destruction, resulting in sustained insulin deficiency and progressive diabetic complications [13, 14].

Both fenofibrate and atorvastatin significantly improved fasting blood glucose and HbA1c levels compared with untreated diabetic rats. Although neither treatment completely normalized glycemic indices, the observed improvement may reflect indirect enhancement of insulin sensitivity, reduction of oxidative stress, and improvement of cellular metabolic homeostasis. Similar observations have been reported by Chen et al. [11] and Lee et al. [8], who demonstrated partial improvement in glucose metabolism following fenofibrate and atorvastatin therapy.

Diabetic nephropathy is characterized by progressive deterioration of renal function. In agreement with previous studies, untreated diabetic rats showed significant elevations in serum urea, serum creatinine, and urinary albumin/creatinine ratio, indicating glomerular and tubular dysfunction [3, 5]. Treatment with fenofibrate and atorvastatin significantly improved these parameters, suggesting preservation of renal filtration capacity and attenuation of diabetes-induced renal injury.

The renoprotective effect of fenofibrate is likely mediated through activation of peroxisome proliferator-activated receptor-α (PPAR-α), resulting in enhanced fatty acid oxidation, reduced renal lipid accumulation, suppression of inflammatory cytokines, and inhibition of profibrotic signaling pathways [10, 11]. Atorvastatin exerts similar protective effects through inhibition of HMG-CoA reductase together with antioxidant, anti-inflammatory, endothelial-protective, and nitric oxide-mediated mechanisms independent of cholesterol reduction [8, 9].

Hypercholesterolemia has been recognized as an important contributor to diabetic kidney disease through renal lipotoxicity and activation of oxidative stress pathways. The present study demonstrated a significant increase in total cholesterol levels in diabetic rats, while both fenofibrate and atorvastatin significantly reduced cholesterol concentrations. High-dose fenofibrate produced the greatest lipid-lowering effect, which is consistent with the pharmacological action of PPAR-α agonists in enhancing lipid metabolism and reducing triglyceride-rich lipoproteins [12].

Histopathological examination supported the biochemical findings. Diabetic control rats exhibited marked glomerular shrinkage, tubular degeneration, vascular congestion, widening of Bowman's space, and inflammatory cell infiltration. These structural abnormalities were markedly attenuated following treatment with fenofibrate and atorvastatin. High-dose fenofibrate demonstrated the greatest histological improvement, suggesting a dose-dependent renoprotective effect. Similar findings have been reported by Olukman et al. [15], who observed significant preservation of renal architecture following fenofibrate treatment in diabetic rats.

Oxidative stress is considered one of the central mechanisms underlying diabetic renal injury. In the present study, diabetic rats demonstrated increased renal MDA levels together with decreased GPx and SOD activities, indicating excessive reactive oxygen species production and impaired antioxidant defense. Administration of fenofibrate and atorvastatin significantly restored antioxidant enzyme activities while reducing lipid peroxidation. High-dose fenofibrate exhibited superior antioxidant activity, suggesting that suppression of oxidative stress is a major contributor to its renoprotective effect. These observations are consistent with previous studies demonstrating antioxidant properties of both drugs in experimental diabetic nephropathy [7, 14, 15].

Pearson correlation analysis further demonstrated strong positive correlations between histopathological injury scores and fasting blood glucose, HbA1c, serum creatinine, urinary albumin/creatinine ratio, total cholesterol, and MDA levels. In contrast, GPx and SOD activities showed significant negative correlations with renal injury scores, emphasizing the close relationship between oxidative stress, renal dysfunction, and structural kidney damage.

Overall, the present findings suggest that fenofibrate and atorvastatin attenuate diabetic nephropathy through multiple complementary mechanisms involving improvement of glycemic status, correction of dyslipidemia, suppression of oxidative stress and inflammation, and preservation of renal histological integrity. High-dose fenofibrate demonstrated the greatest overall efficacy, indicating that activation of PPAR-α may provide additional renoprotective benefits beyond conventional lipid lowering.

Despite these promising findings, the present study has several limitations. The relatively small sample size, short duration of follow-up, and absence of molecular markers of inflammation and fibrosis may limit the generalizability of the results. Future studies incorporating cytokine profiling, immunohistochemistry, and gene expression analysis are warranted to further elucidate the molecular mechanisms responsible for the observed renoprotective effects.

REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas. 11th ed. Brussels: International Diabetes Federation; 2025.

[2] American Diabetes Association. Standards of Care in Diabetes—2025. Diabetes Care. 2025;48(Suppl 1):S1–S350.

[3] Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017;12:2032–2045.

[4] Thomas MC, Brownlee M, Susztak K, et al. Diabetic kidney disease. Nat Rev Dis Primers. 2015;1:15018.

[5] Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013; 93:137–188.

[6] Tuttle KR, Brosius FC, Cavender MA, et al. SGLT2 inhibition for CKD and cardiovascular disease in type 2 diabetes. Kidney Int. 2021; 99:245–255.

[7] Mima A. Inflammation and oxidative stress in diabetic nephropathy. J Diabetes Res. 2013; 2013:248563.

[8] Lee TM, Lin MS, Tsai CH, Chang NC. Atorvastatin improves renal injury and oxidative stress in diabetic rats. Eur J Pharmacol. 2007;584:402–409.

[9] Goldfine AB. Statins: is it really time to reassess benefits and risks? N Engl J Med. 2012; 366:1752–1755.

[10] Ghosh SS, Gehr TW, Ghosh S, Khazaei M. PPAR-α and diabetic nephropathy. PPAR Res. 2010; 2010:605618.

[11] Chen Y, Liu Y, Wang Y, et al. Fenofibrate attenuates diabetic nephropathy through suppression of TGF-β/Smad signaling. Mol Med Rep. 2018; 17:4373–4380.

[12] Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy in patients with type 2 diabetes mellitus (FIELD study). Lancet. 2005;366:1849–1861.

[13] Furman BL. Streptozotocin-induced diabetic models in mice and rats. Curr Protoc Pharmacol. 2021;95: e78.

[14] Yaribeygi H, Atkin SL, Sahebkar A. A review of the molecular mechanisms of diabetic nephropathy. J Cell Physiol. 2019;234(8):12100-12112.

[15] Olukman M, Sezer ED, Ulker S, et al. Fenofibrate treatment improves endothelial dysfunction and attenuates renal injury in experimental diabetes. Eur J Pharmacol. 2010;648(1-3):162-167.