

Original article

Hepatoprotective, Nephroprotective, and Antioxidant Effects of Coenzyme Q10 and Metformin in Streptozotocin-Induced Diabetic Rats: A Dose-Dependent Evaluation

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ABSTRACT

Diabetes mellitus is associated with progressive metabolic derangement, oxidative stress and multi-organ damage. The present study assessed the dose-related effects of coenzyme Q10 (CoQ10) on glycemic control, lipid profile, hepatic and renal function, and tissue oxidative stress in streptozotocin (STZ)-induced diabetic rats, using metformin as a reference drug. Thirty-six male Sprague-Dawley rats were allocated equally to six groups (n = 6): normal control, diabetic control, diabetic + CoQ10 100 mg/kg/day, diabetic + CoQ10 200 mg/kg/day, normal + CoQ10 200 mg/kg/day, and diabetic + metformin 200 mg/kg/day. Diabetes was induced by a single intraperitoneal injection of STZ (55 mg/kg), and treatments were given orally for 8 weeks. All parameters responded to CoQ10 in a dose-related manner. At 200 mg/kg/day, fasting glucose fell to 198.7 ± 12.3 mg/dL, HOMA-IR to 4.45 ± 0.29 , total cholesterol to 181.6 ± 8.7 mg/dL, ALT to 46.2 ± 3.4 U/L, serum creatinine to 1.04 ± 0.07 mg/dL, and hepatic malondialdehyde to 4.2 ± 0.3 nmol/mg protein (all $p < 0.05$ versus diabetic controls), and none of these values differed significantly from those of the metformin group ($p > 0.05$). The 100 mg/kg/day dose produced intermediate improvements. CoQ10 did not alter any parameter in healthy animals ($p > 0.05$). These findings indicate that CoQ10 exerts a broad, dose-related protective effect against STZ-induced metabolic, hepatic, renal and oxidative abnormalities in rats, comparable in magnitude to metformin at the higher dose.

Keywords: Coenzyme Q10; streptozotocin; diabetes mellitus; oxidative stress; hepatoprotection; nephroprotection; dyslipidemia; HOMA-IR; antioxidant enzymes.

1-INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both, together with disturbances of carbohydrate, lipid and protein metabolism. Its burden continues to rise: according to the IDF Diabetes Atlas, 11th edition, 589 million adults aged 20–79 years were living with diabetes worldwide in 2024, a number projected to reach 853 million by 2050, with about 90% of cases being type 2 diabetes and more than 80% of affected individuals living in low- and middle-income countries. Diabetes-related health expenditure exceeded one trillion US dollars in 2024, and the disease accounted for more than 3.4 million deaths (International Diabetes Federation, 2025).

Among the animal models used to study the pathogenesis of diabetes, the STZ-induced diabetic rat is the most widely accepted. STZ, a glucosamine-nitrosourea antibiotic produced by *Streptomyces achromogenes*, selectively destroys pancreatic β -cells through alkylation of their DNA, excessive generation of reactive oxygen species (ROS) and activation of poly(ADP-ribose) polymerase, culminating in β -cell death and profound insulin deficiency (Furman, 2021; Arenas et al., 2023). The resulting hypoinsulinemic state reproduces the metabolic abnormalities seen in human diabetes, including hyperglycemia, increased lipolysis and muscle protein catabolism, dyslipidemia and progressive oxidative organ damage (Furman, 2021).

Oxidative stress is central to the pathophysiology of this model. Once β -cell destruction has established insulin deficiency, chronic hyperglycemia drives ROS overproduction through glucose auto-oxidation, uncoupling of the mitochondrial electron transport chain, and activation of the polyol and hexosamine pathways (Samimi et al., 2024a). This is reflected in increased malondialdehyde (MDA), a marker of lipid peroxidation, and decreased superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and reduced glutathione (GSH), which together constitute the antioxidant defense system (Samimi et al., 2024a; Mahmoud et al., 2023). The resulting redox imbalance injures hepatocytes, manifesting as elevated serum transaminases and impaired hepatic synthetic function, and impairs renal function, manifesting as reduced glomerular filtration with elevated serum creatinine, urea and uric acid (Mahmoud et al., 2023; Kirkman et al., 2023). In parallel, insulin deficiency in STZ-diabetic rats pro-

duces a highly atherogenic lipid profile because lipolysis is no longer suppressed and lipoprotein lipase activity is reduced.

Coenzyme Q10 (CoQ10, ubiquinone) is an endogenously synthesized, lipid-soluble antioxidant and an essential cofactor of the mitochondrial electron transport chain; in its reduced form it efficiently scavenges lipid peroxyl radicals and regenerates other antioxidants such as vitamin E (Hargreaves, 2021). CoQ10 levels are reduced in the diabetic state, and several recent studies have clarified the mechanisms by which supplementation may prevent diabetic organ damage. In the liver, CoQ10 activates the cytoprotective Nrf2/Keap1/HO-1 pathway under hyperglycemia-induced oxidative stress (Samimi et al., 2024b) and stimulates AMPK signaling, thereby repressing lipogenic genes (SREBP-1c, ACC, FAS) and promoting fatty-acid β -oxidation through PPAR α /CPT-1 (Chen et al., 2019; Liang et al., 2022). In the pancreas, CoQ10 helps preserve β -cell structure and function through the miR-33a/miR-21/SREBP1 axis (Adachi et al., 2025) and prevents β -cell apoptosis by blocking mitochondrial cytochrome c release and caspase-3 activation (Ogasahara et al., 2018). Renal studies indicate that CoQ10 attenuates tubular oxidative injury and preserves glomerular filtration in experimental diabetic nephropathy (Lakshmanan & Watanabe, 2020; Adeoye et al., 2024), and its renoprotective mechanisms are the subject of a registered systematic review (Buondonno et al., 2024). In humans, a 2024 umbrella review concluded that CoQ10 produces a clinically meaningful improvement in glycemic indices such as fasting glucose and HbA1c, with the largest effects in individuals with diabetes or metabolic impairment (Martínez-Lapiscina et al., 2024), and meta-analyses have reported significant improvements in lipid profile (Dludla et al., 2023) and liver enzymes (Soleimani Damaneh et al., 2023; Ardekani et al., 2023).

Despite this body of evidence, most studies have examined the effect of CoQ10 on a single organ or pathway, or at a single dose, and rarely in direct comparison with a standard antidiabetic drug. A head-to-head comparison of two CoQ10 doses with a first-line agent such as metformin, covering glycemic, lipid, hepatic, renal and oxidative-stress endpoints in the same animals, has not previously been reported. The present study therefore evaluated the dose-related effects of CoQ10 (100 and 200 mg/kg/day) in comparison with metformin in STZ-induced diabetic rats.

2-MATERIALS AND METHODS

Animals and housing

Thirty-six male Sprague-Dawley rats aged 8 weeks were obtained from the institutional animal house. Animals were housed in standard polypropylene cages at 22 ± 2 °C under a 12 h light/12 h dark cycle, with free access to a standard commercial pellet diet and tap water, and were acclimatized for one week before any procedure. All experimental protocols complied with the guidelines for the care and use of laboratory animals and were approved by the institutional ethics committee (approval number: [to be inserted]).

Experimental design

After acclimatization, rats were randomly allocated to six equal groups (n = 6), as summarized in Table 1. CoQ10 was suspended in corn oil and metformin dissolved in distilled water; all treatments were given once daily by oral gavage for 8 consecutive weeks after confirmation of diabetes (Nabi et al., 2013). Control animals received the corresponding vehicle.

Table 1: Experimental groups and treatments.

Group	Diabetic status	Treatment (oral gavage, once daily, 8 weeks)	Reference
G1: Normal control	Non-diabetic	Corn oil (vehicle)	Fouad & Jresat, 2012
G2: Diabetic control	STZ-diabetic	Corn oil (vehicle)	Eleazu et al., 2013
G3: Diabetic + CoQ10 low dose	STZ-diabetic	CoQ10 100 mg/kg/day in corn oil	Fouad et al., 2014
G4: Diabetic + CoQ10 high dose	STZ-diabetic	CoQ10 200 mg/kg/day in corn oil	Fouad et al., 2014
G5: Normal + CoQ10 high dose	Non-diabetic	CoQ10 200 mg/kg/day in corn oil	Fouad et al., 2014
G6: Diabetic + metformin	STZ-diabetic	Metformin 200 mg/kg/day in distilled water	Naghdi et al., 2022

STZ = streptozotocin; CoQ10 = coenzyme Q10.

Induction of experimental diabetes

Diabetes was induced in groups 2, 3, 4 and 6 by a single intraperitoneal injection of STZ (55 mg/kg body weight) freshly dissolved in cold 0.1 M sodium citrate buffer, pH 4.5 (Eleazu et al., 2013). Rats in groups 1 and 5 received an equivalent volume of citrate buffer. To prevent STZ-induced hypoglycemia during the first 24 h, STZ-injected

rats were given 10% glucose in their drinking water overnight (Damasceno et al., 2014). Seventy-two hours after STZ injection, fasting blood glucose was measured in tail-vein blood with a calibrated glucometer; rats with fasting glucose ≥ 200 mg/dL were considered diabetic and included (Eleazu et al., 2013; Damasceno et al., 2014). Animals not meeting this criterion were excluded and replaced.

Body weight and fasting blood glucose monitoring

Body weight and fasting blood glucose were recorded at baseline (before STZ injection) and weekly throughout the 8-week treatment period (Nabi et al., 2013). Fasting glucose was measured after a 12 h fast in tail-vein blood using a calibrated glucometer based on the glucose oxidase principle (Trinder, 1969).

Sample collection

At the end of the treatment period, rats were fasted for 12 h and anesthetized with an intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg) (Smiler et al., 1990). Blood was collected by cardiac puncture into plain and EDTA tubes. Plain-tube samples were allowed to clot at room temperature and centrifuged at 3000 rpm for 15 min; the serum was stored at -20°C until analysis. The liver, kidneys and pancreas were then rapidly excised, rinsed in ice-cold saline and snap-frozen at -80°C for biochemical assays.

Biochemical analyses

All biochemical measurements were performed in duplicate. Serum glucose was determined by the glucose oxidase method (Trinder, 1969). Serum insulin was measured with a rat-specific ELISA kit (Elabscience Biotechnology Co., Ltd., Wuhan, China; Cat. No. E-EL-R0558) according to the manufacturer's instructions, and insulin resistance was estimated by the homeostatic model assessment (HOMA-IR) as fasting glucose (mmol/L) $\times$ fasting insulin ($\mu\text{IU/mL}$)/22.5 (Matthews et al., 1985). Total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were measured with enzymatic colorimetric kits (Spinreact S.A.U., Girona, Spain) (Fossati & Prencipe, 1982); low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) were calculated by the Friedewald equation, $\text{LDL-C} = \text{TC} - \text{HDL-C} - \text{TG}/5$ and $\text{VLDL-C} = \text{TG}/5$ (Friedewald et al., 1972). Hepatic function was assessed by serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin and albumin, and renal function by serum creatinine, blood urea nitrogen (BUN), uric acid and total protein, using colorimetric kits (Biodiagnostic Co., Cairo, Egypt) according to the manufacturer's instructions (Reitman & Frankel, 1957; Bartels et al., 1972). All ELISA-based assays (insulin, MDA, SOD, CAT, GPx and GSH) were read at 450 nm on a microplate reader (Epoch, BioTek/Agilent Technologies, Santa Clara, CA, USA), and concentrations were derived from the standard curve constructed for each assay.

Assessment of oxidative stress markers

Liver and kidney tissues were homogenized in ice-cold phosphate buffer (pH 7.4) and centrifuged at $10,000 \times g$ for 15 min at 4°C ; the supernatant was used for analysis. Lipid peroxidation was assessed as MDA using a rat MDA ELISA kit (Elabscience; Cat. No. E-EL-0060, lot E23640), based on the thiobarbituric acid reaction (Ohkawa et al., 1979). SOD activity was determined with a rat SOD ELISA kit (Elabscience; Cat. No. E-EL-0044, lot E15645) (Marklund & Marklund, 1974), CAT activity with a rat CAT ELISA kit (MyBioSource Inc., San Diego, CA, USA; Cat. No. MBS2507174, lot E44896), GPx activity with a rat GPx ELISA kit (Elabscience; Cat. No. E-EL-0056, lot E20167) (Paglia & Valentine, 1967), and GSH with a rat GSH ELISA kit (MyBioSource; Cat. No. MBS2507227, lot E62676), all according to the manufacturers' instructions. Protein concentration in the homogenates was determined by the Bradford method (Bradford, 1976), and results are expressed per milligram of protein.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation (SD). Differences among groups were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons (Tukey, 1949), using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant. Because only two CoQ10 doses were tested, the term "dose-related" refers to the pairwise comparison between the 100 and 200 mg/kg groups and not to a formal dose-response (trend) analysis; likewise, the absence of a significant difference between CoQ10 and metformin indicates that no difference was detected in this sample and does not establish statistical equivalence, which would require a dedicated equivalence test.

3-RESULTS

Body weight

Initial body weights did not differ among groups (Table 2). Diabetic control rats (G2) had a significantly lower final body weight than normal controls (178.4 ± 6.8 vs. 245.6 ± 7.4 g; $p < 0.05$). CoQ10 increased final body weight in a dose-related manner, G4 being superior to G3 ($p < 0.05$ for both versus G2), although neither dose restored body weight to the level of G1. The final body weight of G4 did not differ from that of the metformin group (220.7

± 7.6 g; $p > 0.05$), and G5 did not differ from G1 ($p > 0.05$).

Table 2: Effect of CoQ10 supplementation and metformin on initial and final body weight in STZ-induced diabetic rats (mean $\pm$ SD, n = 6).

Group	Initial body weight (g)	Final body weight (g)
G1: Normal control	180.3 $\pm$ 5.2	245.6 $\pm$ 7.4
G2: Diabetic control	179.8 $\pm$ 4.9	178.4 $\pm$ 6.8
G3: Diabetic + CoQ10 100 mg/kg	180.1 $\pm$ 5.6	198.3 $\pm$ 7.1
G4: Diabetic + CoQ10 200 mg/kg	179.6 $\pm$ 4.8	215.4 $\pm$ 6.9
G5: Normal + CoQ10 200 mg/kg	180.5 $\pm$ 5.1	248.2 $\pm$ 8.1
G6: Diabetic + Metformin	179.9 $\pm$ 5.3	220.7 $\pm$ 7.6

Final body weight: $G2 < G3 < G4 \approx G6 < G1 \approx G5$ ($p < 0.05$ for each ordered difference; one-way ANOVA with Tukey's test).

Glycemic control

Diabetic control rats showed markedly elevated fasting glucose, reduced serum insulin and increased HOMA-IR compared with normal controls (all $p < 0.05$; Table 3). Both CoQ10 doses significantly improved all three parameters relative to G2, and the 200 mg/kg dose was significantly more effective than 100 mg/kg ($p < 0.05$ for each), although neither dose restored the values to those of G1. Fasting glucose, insulin and HOMA-IR in G4 did not differ significantly from those in the metformin group ($p > 0.05$). In non-diabetic rats, CoQ10 (G5) had no effect on any glycemic variable compared with G1 ($p > 0.05$).

Table 3: Effect of CoQ10 supplementation on fasting blood glucose, serum insulin and HOMA-IR in STZ-induced diabetic rats (mean $\pm$ SD, n = 6).

Group	Fasting blood glucose (mg/dL)	Serum insulin (μ IU/mL)	HOMA-IR
G1: Normal control	89.4 $\pm$ 4.2 ^a	12.8 $\pm$ 1.4 ^a	2.83 $\pm$ 0.31 ^d
G2: Diabetic control	389.6 $\pm$ 18.7 ^d	3.2 $\pm$ 0.6 ^d	7.74 $\pm$ 0.42 ^a
G3: Diabetic + CoQ10 100 mg/kg	298.3 $\pm$ 15.4 ^c	6.4 $\pm$ 0.9 ^c	5.92 $\pm$ 0.38 ^b
G4: Diabetic + CoQ10 200 mg/kg	198.7 $\pm$ 12.3 ^b	9.1 $\pm$ 1.1 ^b	4.45 $\pm$ 0.29 ^c
G5: Normal + CoQ10 200 mg/kg	87.6 $\pm$ 3.9 ^a	13.1 $\pm$ 1.6 ^a	2.79 $\pm$ 0.28 ^d
G6: Diabetic + Metformin	187.4 $\pm$ 11.8 ^b	9.6 $\pm$ 1.2 ^b	4.21 $\pm$ 0.33 ^c

Different superscript letters within a column indicate significant differences between groups ($p < 0.05$; one-way ANOVA followed by Tukey's post hoc test); groups sharing a letter do not differ significantly. HOMA-IR = homeostatic model assessment of insulin resistance.

Lipid profile

Diabetic control rats developed a markedly atherogenic lipid profile, with significantly higher TC, TG, LDL-C and VLDL-C and lower HDL-C than normal controls (all $p < 0.05$; Table 4). Both CoQ10 doses significantly improved all five parameters compared with G2, and G4 was superior to G3 for each parameter ($p < 0.05$), without full normalization to G1 values. No lipid parameter differed significantly between G4 and G6 ($p > 0.05$). CoQ10 did not alter the lipid profile of non-diabetic rats (G5 vs. G1, $p > 0.05$).

Table 4: Effect of CoQ10 supplementation on serum lipid profile in STZ-induced diabetic rats (mean $\pm$ SD, n = 6).

Group	TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	VLDL-C (mg/dL)
G1: Normal control	142.3 $\pm$ 6.4 ^d	98.4 $\pm$ 5.1 ^d	52.6 $\pm$ 3.2 ^a	69.9 $\pm$ 4.1 ^d	19.7 $\pm$ 1.8 ^d
G2: Diabetic control	268.7 $\pm$ 12.3 ^a	224.6 $\pm$ 11.8 ^a	24.3 $\pm$ 2.1 ^d	199.5 $\pm$ 9.8 ^a	44.9 $\pm$ 3.2 ^a
G3: Diabetic + CoQ10 100 mg/kg	221.4 $\pm$ 10.1 ^b	178.3 $\pm$ 9.4 ^b	34.7 $\pm$ 2.6 ^c	151.1 $\pm$ 8.3 ^b	35.7 $\pm$ 2.8 ^b
G4: Diabetic + CoQ10 200 mg/kg	181.6 $\pm$ 8.7 ^c	138.2 $\pm$ 7.6 ^c	44.2 $\pm$ 3.1 ^b	109.8 $\pm$ 6.9 ^c	27.6 $\pm$ 2.1 ^c
G5: Normal + CoQ10 200 mg/kg	139.8 $\pm$ 5.9 ^d	96.1 $\pm$ 4.8 ^d	53.4 $\pm$ 3.4 ^a	67.2 $\pm$ 3.8 ^d	19.2 $\pm$ 1.6 ^d
G6: Diabetic + Metformin	178.2 $\pm$ 8.2 ^c	134.6 $\pm$ 7.1 ^c	45.8 $\pm$ 3.3 ^b	105.6 $\pm$ 6.4 ^c	26.9 $\pm$ 1.9 ^c

Different superscript letters within a column indicate significant differences between groups ($p < 0.05$; one-way ANOVA followed by Tukey's post hoc test). TC = total cholesterol; TG = triglycerides; HDL-C, LDL-C, VLDL-C = high-, low- and very-low-density lipoprotein cholesterol.

Hepatic function

Serum ALT, AST, ALP and total bilirubin were significantly elevated, and albumin significantly reduced, in diabetic control rats compared with normal controls (all $p < 0.05$; Table 5). CoQ10 at both doses significantly improved every hepatic parameter relative to G2, with 200 mg/kg superior to 100 mg/kg ($p < 0.05$ for all). None of the hepatic indices in G4 differed significantly from those in G6 ($p > 0.05$), and none differed between G5 and G1 ($p > 0.05$).

Table 5: Effect of CoQ10 supplementation on hepatic function markers in STZ-induced diabetic rats (mean $\pm$ SD, n = 6).

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Albumin (g/dL)
G1: Normal control	28.4 $\pm$ 2.1 ^d	32.6 $\pm$ 2.4 ^d	68.3 $\pm$ 4.2 ^d	0.42 $\pm$ 0.04 ^d	4.21 $\pm$ 0.18 ^a
G2: Diabetic control	89.7 $\pm$ 6.3 ^a	102.4 $\pm$ 7.1 ^a	198.6 $\pm$ 11.4 ^a	1.24 $\pm$ 0.09 ^a	2.64 $\pm$ 0.14 ^d
G3: Diabetic + CoQ10 100 mg/kg	68.3 $\pm$ 4.8 ^b	78.6 $\pm$ 5.4 ^b	154.3 $\pm$ 9.2 ^b	0.94 $\pm$ 0.07 ^b	3.12 $\pm$ 0.16 ^c
G4: Diabetic + CoQ10 200 mg/kg	46.2 $\pm$ 3.4 ^c	54.3 $\pm$ 3.8 ^c	112.4 $\pm$ 7.3 ^c	0.68 $\pm$ 0.05 ^c	3.74 $\pm$ 0.17 ^b
G5: Normal + CoQ10 200 mg/kg	27.1 $\pm$ 1.9 ^d	31.8 $\pm$ 2.2 ^d	66.7 $\pm$ 3.9 ^d	0.40 $\pm$ 0.03 ^d	4.28 $\pm$ 0.19 ^a
G6: Diabetic + Metformin	44.8 $\pm$ 3.2 ^c	52.7 $\pm$ 3.6 ^c	108.9 $\pm$ 6.8 ^c	0.65 $\pm$ 0.05 ^c	3.81 $\pm$ 0.18 ^b

Different superscript letters within a column indicate significant differences between groups ($p < 0.05$; one-way ANOVA followed by Tukey's post hoc test). ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase.

Renal function

Diabetic control rats showed marked elevations in serum creatinine, BUN and uric acid and a substantial fall in total protein compared with normal controls (all $p < 0.05$; Table 6), consistent with impaired glomerular filtration and tubular dysfunction. CoQ10 improved all renal parameters in a dose-related manner: the 100 mg/kg dose produced a moderate but significant improvement, whereas 200 mg/kg reduced creatinine, BUN and uric acid to 1.04 ± 0.07 mg/dL, 28.7 ± 2.4 mg/dL and 3.86 ± 0.28 mg/dL, respectively, and raised total protein to 6.41 ± 0.29 g/dL. No renal marker differed significantly between G4 and the metformin group ($p > 0.05$). CoQ10 had no effect on renal function in non-diabetic rats (G5 vs. G1, $p > 0.05$).

Table 6: Effect of CoQ10 supplementation on renal function markers in STZ-induced diabetic rats (mean $\pm$ SD, n = 6).

Group	Creatinine (mg/dL)	BUN (mg/dL)	Uric acid (mg/dL)	Total protein (g/dL)
G1: Normal control	0.62 $\pm$ 0.04 ^d	18.4 $\pm$ 1.6 ^d	2.84 $\pm$ 0.22 ^d	7.42 $\pm$ 0.31 ^a
G2: Diabetic control	1.89 $\pm$ 0.12 ^a	54.6 $\pm$ 4.2 ^a	6.78 $\pm$ 0.48 ^a	4.18 $\pm$ 0.24 ^d
G3: Diabetic + CoQ10 100 mg/kg	1.42 $\pm$ 0.09 ^b	40.3 $\pm$ 3.1 ^b	5.12 $\pm$ 0.36 ^b	5.34 $\pm$ 0.27 ^c
G4: Diabetic + CoQ10 200 mg/kg	1.04 $\pm$ 0.07 ^c	28.7 $\pm$ 2.4 ^c	3.86 $\pm$ 0.28 ^c	6.41 $\pm$ 0.29 ^b
G5: Normal + CoQ10 200 mg/kg	0.60 $\pm$ 0.03 ^d	17.9 $\pm$ 1.4 ^d	2.79 $\pm$ 0.19 ^d	7.48 $\pm$ 0.33 ^a
G6: Diabetic + Metformin	1.01 $\pm$ 0.06 ^c	27.4 $\pm$ 2.2 ^c	3.74 $\pm$ 0.26 ^c	6.54 $\pm$ 0.30 ^b

Different superscript letters within a column indicate significant differences between groups ($p < 0.05$; one-way ANOVA followed by Tukey's post hoc test). BUN = blood urea nitrogen.

Oxidative stress markers in liver and kidney

Oxidative stress parameters in liver and kidney tissue are shown in Figures 1 and 2, respectively. Diabetic control rats had significantly higher MDA and significantly lower SOD, CAT, GPx and GSH than normal controls in both tissues ($p < 0.05$ for all). CoQ10 at both doses significantly improved every parameter in both tissues compared with G2, and the 200 mg/kg dose was significantly more effective than 100 mg/kg ($p < 0.05$ for each), although neither dose restored the values to those of G1. Hepatic and renal oxidative stress markers in G4 did not differ significantly from those in the metformin group ($p > 0.05$), and CoQ10 did not alter the redox status of non-diabetic rats (G5 vs. G1, $p > 0.05$).

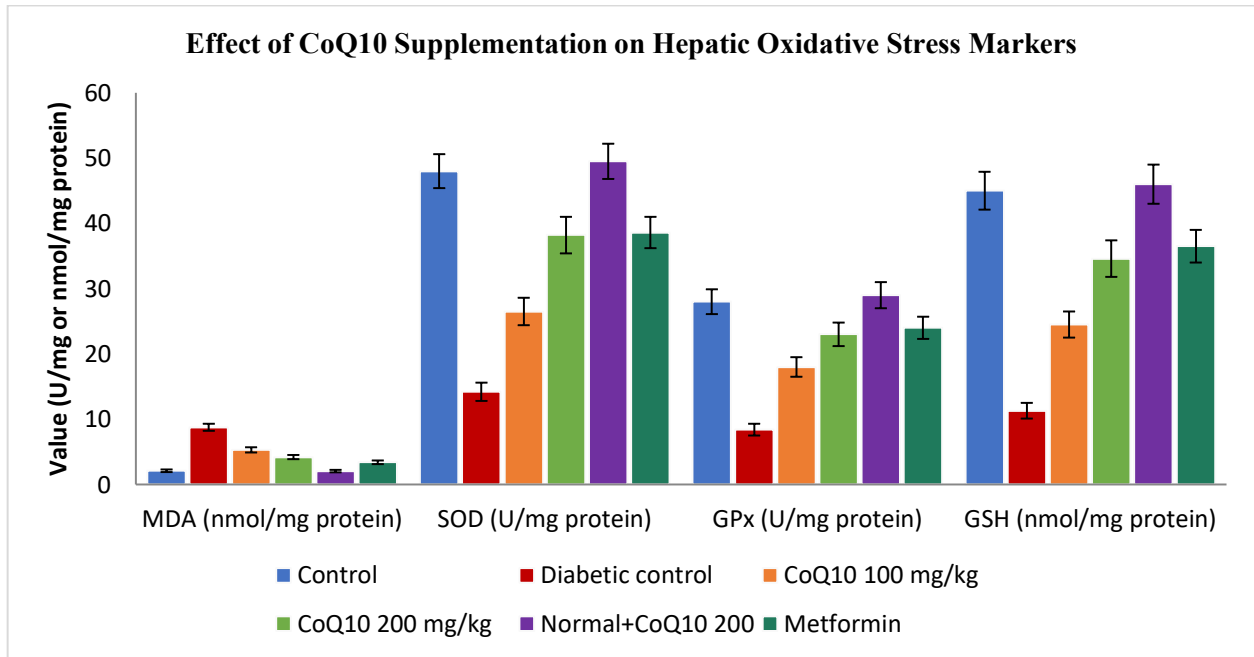


Figure 1: Effect of CoQ10 supplementation on oxidative stress markers (MDA, SOD, GPx and GSH) in liver tissue of STZ-induced diabetic rats. Values are means (n = 6).

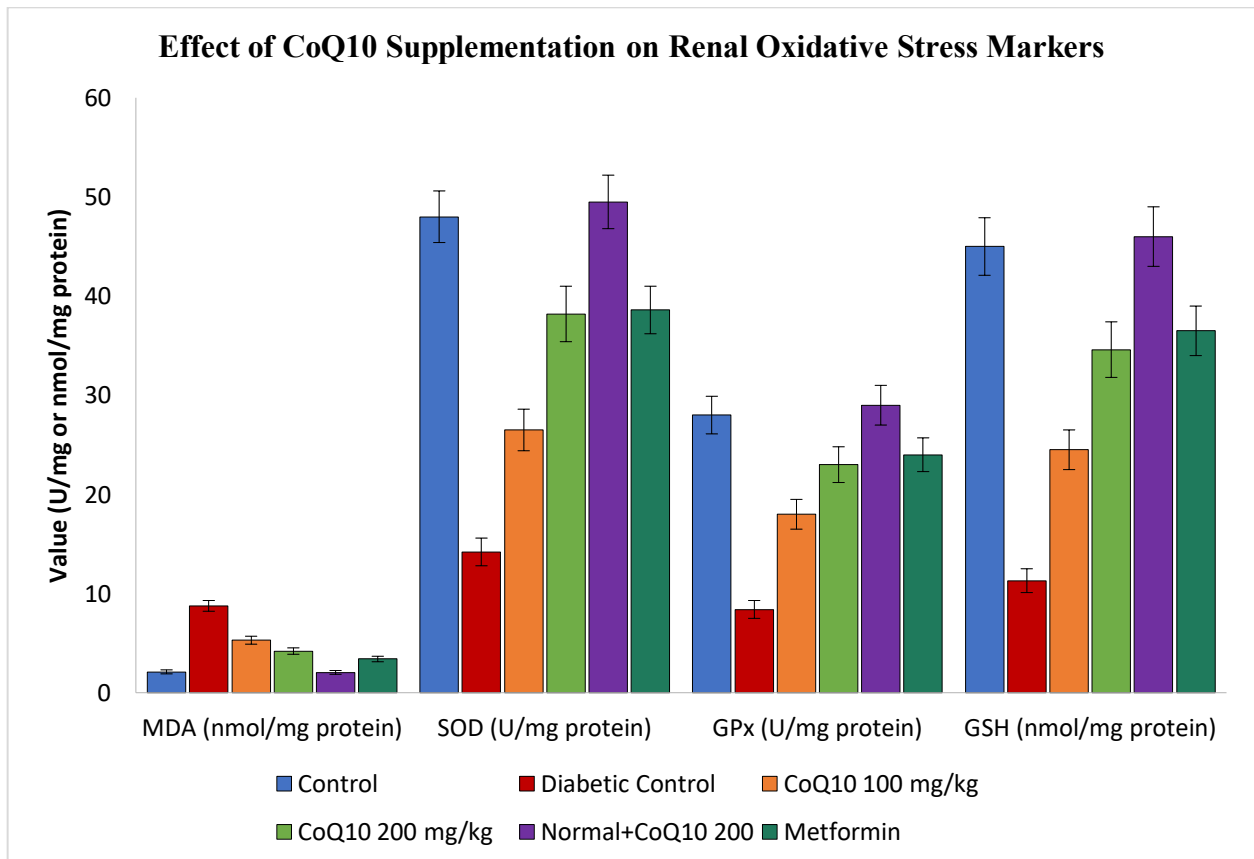


Figure 2: Effect of CoQ10 supplementation on oxidative stress markers (MDA, SOD, GPx and GSH) in kidney tissue of STZ-induced diabetic rats. Values are means (n = 6).

4-DISCUSSION

In the present study, CoQ10 at 100 and 200 mg/kg/day produced a dose-related protective effect against STZ-induced alterations in body weight, glucose homeostasis, lipid profile, hepatic and renal function, and tissue oxidative stress, and the higher dose was as effective as metformin for every parameter examined. These data agree with previous experimental studies, although they must be interpreted against a background of inconsistent clinical evidence, as discussed below.

The weight loss of diabetic rats reflects the catabolic consequences of STZ-induced insulin deficiency, which stimulates lipolysis and muscle protein breakdown (Furman, 2021). The weight gain observed with CoQ10 agrees with the findings of Tan et al. (2023) in a high-fat diet/STZ rat model and is consistent with the glucose-lowering effect observed here, since reduced glucotoxicity lessens catabolism; the present design cannot, however, determine whether the weight gain resulted from a direct action of CoQ10 or from improved glycemic control.

CoQ10 lowered fasting glucose and HOMA-IR and partially restored insulin in a dose-related manner. This is directionally consistent with several animal studies and with a 2024 umbrella review that reported small but detectable improvements in fasting glucose and HbA1c after CoQ10 supplementation in diabetic populations (Martínez-Lapiscina et al., 2024). The clinical evidence is not unanimous, however: a meta-analysis of randomized trials found no benefit of CoQ10 on glycemic control in diabetic patients (Suksomboon et al., 2015), and a controlled human study showed that CoQ10 did not improve peripheral insulin sensitivity, muscle GLUT4 expression or insulin secretory capacity, although it modestly improved hepatic insulin sensitivity (Kuhlman et al., 2019). Such discrepancies may reflect the pharmacological doses used in rodents (100–200 mg/kg/day here, far above human-equivalent doses), the lower doses used in most trials (100–300 mg/day), and differences in baseline CoQ10 status among participants.

Mechanistically, our results are compatible with improved insulin availability, but β -cell mass, apoptotic markers and insulin-signaling components were not measured. Mechanisms proposed elsewhere include preservation of β -cell integrity through miRNA signaling (Adachi et al., 2025) and inhibition of mitochondria-mediated β -cell apoptosis (Ogasahara et al., 2018); either is plausible but neither was tested directly in this study.

A similar dose-related pattern was seen in the lipid panel, with CoQ10 200 mg/kg/day lowering TC, TG and LDL-C and raising HDL-C to levels not significantly different from those achieved with metformin. This agrees with a meta-analysis of 50 randomized trials showing lipid-lowering effects of CoQ10 in adults (Dludla et al., 2023). Contrasting evidence again warrants caution: an earlier meta-analysis found no lipid benefit in diabetic patients (Suksomboon et al., 2015), and a randomized trial of 150 mg/day CoQ10 in patients with type 2 diabetes reported no significant improvement in the lipid profile despite an effect on glycemic control (Zahedi et al., 2014). The authors attributed such variability to differences in baseline lipid status and treatment duration, indicating that the lipid effects of CoQ10 depend on factors that are not reproduced in rodent models.

Hepatic and renal function markers showed the same dose-related response: CoQ10 200 mg/kg/day significantly attenuated the transaminase elevation, hyperbilirubinemia, hypoalbuminemia and the rises in creatinine, BUN and uric acid seen in diabetic controls, to levels statistically indistinguishable from the metformin group. This agrees with the meta-analysis of CoQ10 effects on liver enzymes (Soleimani Damaneh et al., 2023) and with experimental nephroprotection in the STZ model (Lakshmanan & Watanabe, 2020). Because histopathological examination of liver and kidney was not performed, the improvement can be interpreted only as a reduction of biochemical markers of organ injury rather than as demonstrated structural protection. Activation of the Nrf2/Keap1/HO-1 pathway (Samimi et al., 2024b) and preservation of the mitochondrial permeability transition pore (Adeoye et al., 2024) are plausible underlying mechanisms, but they were not tested here.

The reduction of MDA and the restoration of SOD, CAT, GPx and GSH in liver and kidney can be attributed to the established antioxidant function of CoQ10, which scavenges lipid peroxyl radicals and regenerates other antioxidants (Hargreaves, 2021). Because oxidative stress lies upstream of many of the organ injuries reported above, this antioxidant action may account, at least in part, for the improvement in the other outcomes, and the parallel dose-related pattern across all endpoints supports this integrated interpretation; nevertheless, a causal sequence from reduced oxidative stress to improved organ function cannot be established with the present design.

Overall, these results support a beneficial effect of high-dose CoQ10 in STZ-diabetic rats that is similar in magnitude to that of metformin for all endpoints assessed. Given the discrepancy between these findings and the substantial body of clinical trials reporting no or inconsistent effects on glycemic and lipid markers (Suksomboon et al., 2015; Zahedi et al., 2014; Kuhlman et al., 2019), the results cannot be extrapolated directly to humans and require confirmation in appropriately designed clinical studies.

Study limitations

Several limitations should be acknowledged. First, histopathological examination of liver, kidney and pancreas was not performed, so the biochemical improvements cannot be equated with structural protection. Second, the molecular mechanisms discussed (Nrf2/Keap1/ARE activation, inhibition of β -cell apoptosis) were not evaluated directly and remain inferential. Third, the sample size was small ($n = 6$ per group) and, because only two doses were tested without trend analysis, the dose-related effects rest on a pairwise comparison rather than a formal dose-response relationship; similarly, the comparability of CoQ10 with metformin is based on the absence of a detectable difference rather than on an equivalence test. Fourth, the conclusions regarding safety rest on the biochemical parameters measured and not on a formal toxicological evaluation. Finally, the doses used (100–200 mg/kg/day) ex-

ceed human-equivalent doses, and, given the inconsistent clinical evidence on the glycemic and lipid effects of CoQ10, these findings cannot be translated into clinical efficacy.

5-CONCLUSION

CoQ10 at 100 and 200 mg/kg/day significantly improved STZ-induced abnormalities in glycemic control, lipid profile, hepatic and renal function, and tissue oxidative stress in rats, and the 200 mg/kg/day dose did not differ significantly from metformin for any of these parameters. The improvement was accompanied by recovery of antioxidant enzyme activities (SOD, CAT, GPx) and GSH content and by reduced lipid peroxidation in liver and kidney, pointing to an antioxidant mechanism that was not, however, directly confirmed; involvement of the Nrf2/Keap1/ARE pathway is a plausible route for CoQ10 action that merits future investigation. CoQ10 did not alter any biochemical parameter in non-diabetic rats.

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