4. Results

4.1. Studies on Nephropathy

4.1.1. Effect of coenzyme Q10, metformin or combination of both on body weight and kidney weight

The body weight of the diabetic rats showed a significant (P < 0.001) decrease after the administration of STZ-nicotinamide. The treatment with coenzyme Q10 or metformin or coenzyme Q10 + metformin did not show any reduction in the body weight as compared with diabetic control rats.

There was a significant (P < 0.001) increase in kidney weight after 6th week in diabetic control rats as compared to normal control rats, while the treatment with coenzyme Q10 or metformin or coenzyme Q10 + metformin showed a significant (P < 0.01; P < 0.01; P < 0.001) reduction in kidney weight as compared to diabetic control rats (Table 2).

**Table 2: Effect of coenzyme Q10, metformin or combination of both on body weight and kidney weight**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial body weight (g)</th>
<th>Final body weight (g)</th>
<th>Kidney weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (a)</td>
<td>235.0 ± 5.28</td>
<td>255.0 ± 5.21</td>
<td>0.59 ± 0.01</td>
</tr>
<tr>
<td>Diabetic control (b)</td>
<td>271.7 ± 9.14</td>
<td>186.7 ± 11.5</td>
<td>1.18 ± 0.06</td>
</tr>
<tr>
<td>Coenzyme Q10 (10 mg/kg) (c)</td>
<td>225.0 ± 8.76</td>
<td>196.7 ± 9.28</td>
<td>0.94 ± 0.02</td>
</tr>
<tr>
<td>Metformin (500 mg/kg) (d)</td>
<td>224.0 ± 8.63</td>
<td>204.0 ± 9.55</td>
<td>0.86 ± 0.02</td>
</tr>
<tr>
<td>Coenzyme Q10 + Metformin (e)</td>
<td>229.7 ± 12.09</td>
<td>212.7 ± 10.38</td>
<td>0.80 ± 0.02</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
4.1.2. Effect of coenzyme Q10, metformin or combination of both on urine volume

In diabetic control group, urine volume was significantly \((P < 0.001)\) increased when compared to the normal control rats. When diabetic rats treated with coenzyme Q10, metformin or coenzyme Q10 + metformin showed a significant \((P < 0.05; P < 0.01\) and \(P < 0.001)\) reduction in urine volume as compared to diabetic control rats, respectively. However, co-administration of coenzyme and metformin showed a greater reduction \((P < 0.05)\) in urine volume levels than when coenzyme Q10 administered singly, but combination of both did not show any significant reduction in urine volume as compared to metformin alone group (Figure 8).

![Graph showing urine volume](image)

**Fig. 8**: Effect of coenzyme Q10, metformin or combination of both on urine volume

Values are expressed as mean ± SEM; n=6

a vs. b, ### \(P < 0.001\);
b vs. c, b vs. d and b vs. e, *\(P < 0.05\), **\(P < 0.01\), ***\(P < 0.001\);
c vs. e, *\(P < 0.05\)
4. Results

4.1.3. Effect of coenzyme Q10, metformin or combination of both on urinary protein

Six week post STZ-nicotinamide injection caused a significant (P < 0.001) increase urinary protein of diabetic rats as compared to normal control rats. The treatment with coenzyme Q10, metformin or coenzyme Q10 + metformin showed a significant (P < 0.01; P < 0.001 and P < 0.001) reduction in urinary protein when compared to diabetic control rats. In contrast, co-administration of coenzyme and metformin showed a greater reduction (P < 0.001; P < 0.01) in urine volume levels than when coenzyme Q10 or metformin administered singly (Figure 9).

![Urinary Protein Graph]

**Fig. 9: Effect of coenzyme Q10, metformin or combination of both on urinary protein**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;

c vs. e, +++P < 0.05; d vs. e, $$$P < 0.01.
4.1.4. **Effect of coenzyme Q10, metformin or combination of both on glycated hemoglobin level**

In the diabetic control rats, glycated hemoglobin levels were significantly (P < 0.001) increased when compared to normal control rats. The diabetic rats treated with coenzyme Q10 showed a significant (P < 0.05) reduction in glycated hemoglobin levels as compared to diabetic control rats. However, the treatment with metformin or coenzyme Q10 + metformin showed more significant (P < 0.001) reduction in glycated hemoglobin levels as compared to diabetic control rats. Moreover, co-administration of coenzyme and metformin showed a greater reduction in glycated hemoglobin levels than when administered singly (Figure 10).

![Glycated hemoglobin](image)

**Fig. 10:** Effect of coenzyme Q10, metformin or combination of both on glycated hemoglobin level

Values are expressed as mean ± SEM; n=6

- a vs. b, ### P < 0.001;
- b vs. c, b vs. d and b vs. e, * P < 0.05, ** P < 0.001;
- c vs. e, +++ P < 0.001; d vs. e, $ P < 0.05
4. Results

4.1.5. Effect of coenzyme Q10, metformin or combination of both on serum creatinine

STZ-nicotinamide injection caused a marked reduction in renal function, as characterized by significant ($P < 0.001$) increase in serum creatinine levels as compared to normal control rats. Thus, these data indicate that a single i.p injection of STZ-nicotinamide impairs kidney functions. Treatment with coenzyme Q10, metformin or coenzyme Q10 + metformin showed a significant ($P < 0.01; P < 0.001$ and $P < 0.001$) reduction in serum creatinine levels as compared to diabetic control rats, respectively. Moreover, the combination of coenzyme Q10 and metformin showed more significant ($P < 0.001; P < 0.01$) reduction in serum creatinine levels than that of mono-therapy (coenzyme Q10 or metformin) (Figure 11).

![Serum creatinine](image)

**Fig. 11:** Effect of coenzyme Q10, metformin or combination of both on serum creatinine

Values are expressed as mean ± SEM; n=6

a vs. b, ### $P < 0.001$;
b vs. c, b vs. d and b vs. e, **$P < 0.01$, ***$P < 0.001$; 
c vs. e, +++$P < 0.001$; d vs. e, $$P < 0.01$
4. Results

4.1.6. Effect of coenzyme Q10, metformin or combination of both on serum urea

STZ-nicotinamide injection caused a significant \( P < 0.001 \) increase in serum urea levels as compared to normal control rats. Treatment with coenzyme Q10, metformin or coenzyme Q10 + metformin showed a significant \( P < 0.01; P < 0.05 \) and \( P < 0.001 \) reduction in serum urea levels as compared to diabetic control rats, respectively. Moreover, there was a significant \( P < 0.05; P < 0.01 \) alteration on serum urea in combination therapy of both (coenzyme Q10 and metformin) than that of mono-therapy (coenzyme Q10 or metformin) (Figure 12).

**Fig. 12: Effect of coenzyme Q10, metformin or combination of both on serum urea**

Values are expressed as mean ± SEM; n=6

a vs. b, \( ### P < 0.001 \);
b vs. c, b vs. d and b vs. e, \( ^* P < 0.05, ^{*} P < 0.01, ^{***} P < 0.001 \);
c vs. e, \( ^{+} P < 0.05 \);
d vs. e, \( ^{$$} P < 0.01 \)
4. Results

4.1.7. Effect of coenzyme Q10, metformin or combination of both on serum uric acid

STZ-nicotinamide injection caused a significant (P < 0.001) increase in serum uric acid levels as compared to normal control rats. Treatment with coenzyme Q10, metformin or coenzyme Q10 + metformin showed a significant (P < 0.01; P < 0.001 and P < 0.001) decreases in uric acid levels as compared to diabetic control rats, respectively. Moreover, co-administration of coenzyme and metformin showed a greater (P < 0.001; P < 0.01) reduction in uric acid levels than when administered singly (Figure 13).

![Serum uric acid graph]

Fig. 13: Effect of coenzyme Q10, metformin or combination of both on serum uric acid

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
c vs. e, +++P < 0.001; d vs. e, $$P < 0.01
4. Results

4.1.8. Effect of coenzyme Q10, metformin or combination of both on total cholesterol

Diabetic untreated rats showed a significant (P < 0.001) increase in serum total cholesterol levels as compared to normal control rats. Treatment with coenzyme Q10 or coenzyme Q10 + metformin showed a significant (P < 0.05) reduction in serum total cholesterol levels as compared to diabetic control rats, while the metformin alone treated rats did not show a significant difference in serum total cholesterol level as compared to diabetic control rats (Figure 14).

![Graph showing total cholesterol levels for different groups](image)

**Fig. 14:** Effect of coenzyme Q10, metformin or combination of both on total cholesterol

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, *P < 0.05.
4. Results

4.1.9. Effect of coenzyme Q10, metformin or combination of both on serum triglyceride

Serum triglyceride levels on STZ-nicotinamide injection were significantly (P < 0.001) increased as compared to normal control rats. Treatment with coenzyme Q10 or metformin showed a significant (P < 0.05) reduction in serum triglyceride levels as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + metformin showed more significant (P < 0.01) reduction in serum triglyceride level as compared to diabetic control rats (Figure 15).

**Fig. 15**: Effect of coenzyme Q10, metformin or combination of both on serum triglyceride

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, * P < 0.05; ** P < 0.01.
4. Results

4.1.10. Effect of coenzyme Q10, metformin or combination of both on HDL-C

STZ-nicotinamide injection showed a significant (P < 0.001) decrease in HDL-C levels as compared to normal control rats. Treatment with coenzyme Q10 or coenzyme Q10 + metformin showed a significant (P < 0.05; P < 0.01) increase in HDL-C levels as compared to diabetic control rats, while the metformin alone treated rats did not show a significant difference in HDL-C levels as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + metformin showed more significant (P < 0.05) increase in HDL-C levels than that of mono-therapy (metformin) (Figure 16).

![Graph showing effect of coenzyme Q10, metformin or combination of both on HDL-C levels](image)

**Fig. 16: Effect of coenzyme Q10, metformin or combination of both on HDL-C**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, *P < 0.05, **P < 0.01;
d vs. e, $P < 0.05
4. Results

4.1.1. Effect of coenzyme Q10, metformin or combination of both on malondialdehyde in renal tissue

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly (P < 0.001) increased in renal tissue of diabetic control rats as compared to non diabetic rats after six weeks of study. The treatment of diabetic rats with coenzyme Q10 or metformin or coenzyme Q10 + metformin showed a significant (P < 0.01; P < 0.05 and P < 0.001) decrease in the levels of MDA as compared to diabetic control rats. However, co-administration of coenzyme and metformin showed a greater (P < 0.05; P < 0.01) reduction in MDA levels than when administered singly (Figure 17).

Fig. 17: Effect of coenzyme Q10, metformin or combination of both on malondialdehyde level in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01, ***P < 0.001;
c vs. e, +P < 0.05; d vs. e, $$$P < 0.01
4. Results

4.1.12. Effect of coenzyme Q10, metformin or combination of both on GSH level in renal tissue

There was a significant (P < 0.001) decrease in the levels of GSH, an endogenous antioxidant in renal tissue as compared to normal control group. In contrast, the treatment with coenzyme Q10 or metformin or coenzyme Q10 + metformin showed a significant (P < 0.001; P < 0.01 and P < 0.001) increase in the levels of GSH as compared to diabetic control rats. However, co-administration of coenzyme and metformin did not show any significant difference in GSH levels as compared to mono-therapy (coenzyme Q10 or metformin) (Figure 18).

![GSH Graph]

Fig. 18: Effect of coenzyme Q10, metformin or combination of both on GSH level in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001
4. Results

4.1.13. Effect of coenzyme Q10, metformin or combination of both on SOD activity in renal tissue

There was a significant (P < 0.001) decrease in the levels of antiperoxidative enzymes (SOD) in renal tissue as compared to normal control group. However, the treatment with coenzyme Q10 or metformin or coenzyme Q10 + metformin showed a significant (P < 0.001; P < 0.05; P<0.001) increase in SOD activities, while the co-administration of both showed a significant (P < 0.01) increase in SOD activities than that of metformin alone treatment (Figure 19).

![Superoxide dismutase](image)

**Fig. 19:** Effect of coenzyme Q10, metformin or combination of both on SOD level in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, *P < 0.05,  ***P < 0.001;
d vs. e, $$P < 0.01
4. Results

4.1.14. Effect of coenzyme Q10, metformin or combination of both on catalase activity in renal tissue

Diabetic rats showed a significant (P < 0.001) reduction in catalase activity as compared to normal control rats. The treatment of diabetic rats with coenzyme Q10 or metformin or coenzyme Q10 + metformin showed a significant (P < 0.001; P < 0.01 and P < 0.001) increase in catalase activity as compared to diabetic control rats, while the co-administration of both showed a significant (P < 0.01) increase in catalase activities than that of metformin alone treatment. Moreover, coenzyme Q10 + metformin treated rats did not show any significant alteration in catalase activity than when coenzyme Q10 administered singly (Figure 20).

![Catalase Graph](image)

Fig. 20: Effect of coenzyme Q10, metformin or combination of both on catalase activity in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, *** P < 0.001;
d vs. e, $$P < 0.01
4. Results

4.1.15. Effect of coenzyme Q10, metformin or combination of both on TNF-α level in renal tissue

Diabetic control rats showed a significant (P < 0.001) increase in inflammatory markers such as renal TNF-α level as compared to normal control rats. The treatment with coenzyme Q10 or metformin or coenzyme Q10 + metformin in STZ-nicotinamide treated rats showed a significant (P < 0.001) reduction in renal TNF-α level when compared to diabetic control rats. However, treatment with coenzyme Q10 + metformin showed more significant (P < 0.05) decrease in renal TNF-α level as compared to diabetic rats treated with metformin alone (Figure 21).

![Tumor necrosis factor-α](image)

**Fig. 21**: Effect of coenzyme Q10, metformin or combination of both on TNF-α in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, ### P < 0.001;
d vs. e, $P < 0.05
4. Results

4.1.16. Effect of coenzyme Q10, metformin or combination of both on TGF-β level in renal tissue

Diabetic control rats showed a significant (P < 0.001) increase in inflammatory markers such as renal TGF-β as compared to normal control rats. The treatment with coenzyme Q10 in STZ-nicotinamide treated rats showed a significant (P < 0.01) reduction in TGF-β in renal tissue when compared to diabetic control rats. However, treatment with metformin or coenzyme Q10 + metformin showed more significant (P < 0.001) decrease in level of TGF-β in renal tissue as compared to diabetic control rats. Co-administration of both did not show any significant changes in TGF-β level as compared to diabetic rats treated with metformin or coenzyme Q10 alone (Figure 22).

Fig. 22: Effect of coenzyme Q10, metformin or combination of both on TGF-β level in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, **P < 0.05, ***P < 0.001
4. Results

4.1.17. Effect of coenzyme Q10, metformin or combination of both on myeloperoxidase (MPO) activity in renal tissue

Diabetic control rats showed a significant ($P < 0.001$) increase in MPO activity as compared to normal control rats. The treatment with coenzyme Q10 in STZ-nicotinamide treated rats showed a significant ($P < 0.05$) reduction in renal MPO activity when compared to diabetic control rats. However, treatment with metformin or coenzyme Q10 + metformin showed more significant ($P < 0.001$) decrease in renal MPO activity as compared to diabetic control rats. However, co-administration of both did not show any significant changes in MPO activity as compared to diabetic rats treated with metformin or coenzyme Q10 alone (Figure 23).

![Myeloperoxidase](image)

**Fig. 23:** Effect of coenzyme Q10, metformin or combination of both on myeloperoxidase (MPO) activity in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### $P < 0.001$;

b vs. c and b vs. e, *$P < 0.05$, ***$P < 0.001$
4.1.18. Effect of coenzyme Q10, metformin or combination of both on nitrite content in renal tissue

Nitrite content was significantly (P < 0.001) increased in renal tissue of diabetic rats as compared to normal control group. The coenzyme Q10 + metformin treatment group showed more significant (P < 0.001) decrease in renal nitrite content as compared to diabetic untreated group, while coenzyme Q10 alone or metformin alone caused a significant (P < 0.01) decrease in renal nitrite content as compared to diabetic rats, but this effect was much lesser than combination therapy (Figure 24).

![Graph showing nitrite content in renal tissue](image)

**Fig. 24: Effect of coenzyme Q10, metformin or combination of both on nitrite content in renal tissue**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;

c vs. e, +P < 0.05; d vs. e, $P < 0.05
4.1.19. Histopathological studies

The architecture of the kidney was disturbed with diabetic control rats as compared to normal structural features of control animal. In the normal control group, the histopathological examination of kidney tissue showed normal appearance of glomerulli and tubules. Renal tissue section of diabetic rats showed glomerulosclerosis ($), tubular vacuolization (*), interstitial fibrosis (+) and thickening of glomerular basement membrane (#). The treatment with coenzyme Q10 or metformin showed moderate glomerular necrosis, interstitial fibrosis, moderate tubular vacuolization and thickening of glomerular basement membrane. However, the treatment with coenzyme Q10 and metformin showed a mild tubular swelling, interstitial fibrosis and thickening of glomerular basement membrane with absence of glomerulosclerosis (Figure 25A-E).
Fig. 25: Light microscopy of kidney tissues from rats (HE stained kidney sections). (A) Control group, (B) Diabetic control group, (C) Coenzyme Q10 (D) Metformin (E) Coenzyme Q10 + Metformin
4. Results

4.2. Studies on Neuropathy

4.2.1. Effect of coenzyme Q10, metformin or combination of both on muscular grip strength

Measurement of muscular grip strength was used to evaluate diabetic neuropathy after streptozotocin-nicotinamide injection. In diabetic control group, muscular grip strength was significantly (P < 0.001) decreased as compared to normal control rats. The treatment of diabetic rats with coenzyme Q10 or metformin showed a significant (P < 0.01) increase in muscular grip strength as compared to diabetic control rats. However, the treatment with coenzyme Q10 + metformin showed more significant (P < 0.001) improvement in the muscular grip strength as compared to diabetic control rats. On the other hand, co-administration of coenzyme and metformin showed a significant (P < 0.01; P < 0.05) increase in muscular grip strength than when coenzyme Q10 or metformin administered singly (Figure 26).

![Muscular grip strength](image)

**Fig. 26:** Effect of coenzyme Q10, metformin or combination of both on muscular grip strength

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
c vs. e, ++P < 0.01; d vs. e, $P < 0.05.
4. Results

4.2.2. Effect of coenzyme Q10, metformin or combination of both on pain sensation (thermal pain)

The paw withdrawal response was measured by the Eddy's hot plate. In diabetic rats, there was a significant (P < 0.001) increase in paw withdrawal response as compared to normal control rats showing significant nerve damage in diabetic animals. The paw withdrawal response of all treated rats on day 42 was significantly decreased as compared with the diabetic control group. The treatment of diabetic rats with coenzyme Q10 or metformin or coenzyme Q10 + metformin showed a significant (P < 0.001; P < 0.01; P < 0.001) decrease in paw withdrawal response as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + metformin showed more significant (P < 0.05) decrease in paw withdrawal response than when metformin administered singly, but the treatment with coenzyme Q10 + metformin did not show any significant changes in paw withdrawal response as compared to mono-therapy (coenzyme Q10) (Figure 27).

![Paw Withdrawal Response](image)

Fig. 27: Effect of coenzyme Q10, metformin or combination of both on pain sensation (thermal pain)

Values are expressed as mean ± SEM; n=6
a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
d vs. e, $P < 0.05.
4. Results

4.2.3. Effect of coenzyme Q10, metformin or combination of both on pain sensation (tail flick)

In diabetic rats, there was a significant ($P < 0.001$) increase in tail flick response as compared to normal control rats. The tail flick response of all treated rats on d 42 was significantly decreased compared with the diabetic control group. The treatment of diabetic rats with coenzyme Q10 showed a significant ($P < 0.01$) decrease in tail flick response as compared to diabetic control rats. However, the treatment with metformin or coenzyme Q10 + metformin showed more significant ($P < 0.001$) decrease in tail flick response as compared to diabetic control rats. On the other hand, co-administration of coenzyme Q10 and metformin showed a significant ($P < 0.01; P < 0.05$) decrease in tail flick response than when administered singly (coenzyme Q10 or metformin) (Figure 28).

![Tail flick response graph](image)

Fig. 28: Effect of coenzyme Q10, metformin or combination of both on pain sensation (tail flick)

Values are expressed as mean ± SEM; n=6
a vs. b, ### $P < 0.001$; b vs. c, b vs. d and b vs. e, **$P < 0.01$, ***$P < 0.001$;
c vs. e, ++$P < 0.01$; d vs. e, $^5P < 0.05$. 


4. Results

4.2.4. Effect of coenzyme Q10, metformin or combination of both on malondialdehyde in sciatic nerve

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly (P < 0.001) increased in sciatic nerve of diabetic control rats as compared to non diabetic rats after six weeks of study. The treatment of diabetic rats with coenzyme Q10 or metformin showed a significant (P < 0.01; P < 0.05) decrease in the levels of MDA as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + metformin showed more significant (P < 0.001) reduction in the levels of MDA levels as compared to diabetic control rats. However, co-administration of coenzyme and metformin has more beneficial effect than when administered singly (Figure 29).

Fig. 29: Effect of coenzyme Q10, metformin or combination of both on malondialdehyde in sciatic nerve

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, * P < 0.05, ** P < 0.01, *** P < 0.001;
4. Results

4.2.5. Effect of coenzyme Q10, metformin or combination of both on SOD activity in sciatic nerve

There was a significant (P < 0.001) decrease in the antiperoxidative enzymes (SOD) in sciatic nerve as compared to normal control group. The treatment of diabetic rats with coenzyme Q10 or metformin or coenzyme Q10 + showed a significant (P < 0.001; P < 0.05; P < 0.001) increase in SOD activities as compared to diabetic control rats, respectively. On the other hand, co-administration of coenzyme Q10 and metformin showed a significant (P < 0.05) increase in SOD activities than when administered singly (coenzyme Q10 or metformin) (Figure 30).

Fig. 30: Effect of coenzyme Q10, metformin or combination of both on SOD activity in sciatic nerve

Values are expressed as mean ± SEM; n=6
a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01, ***P < 0.001;
c vs. e, + P < 0.05; d vs. e, $P < 0.05.
4. Results

4.2.6. Effect of coenzyme Q10, metformin or combination of both on GSH level in sciatic nerve

There was a significant (P < 0.001) decrease in the levels of GSH, an endogenous antioxidant in sciatic nerve as compared to normal control group. The treatment of diabetic rats with coenzyme Q10 or metformin or coenzyme Q10 + metformin showed a significant (P < 0.001; P < 0.01; P < 0.001) increase in the levels of GSH as compared to diabetic control rats, respectively. However, the treatment with coenzyme Q10 + metformin showed a significant (P < 0.05) increase in the levels of GSH levels than that of mono-therapy (metformin), but co-administration of both did not show any significant difference in GSH level in sciatic nerve as compared to coenzyme Q10 alone treatment (Figure 31).

**Fig. 31: Effect of coenzyme Q10, metformin or combination of both on GSH level in sciatic nerve**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
d vs. e, $P < 0.05.
4.2.7. Histopathological studies of sciatic nerve

Histopathology of sciatic nerve in normal control rats showed normal structure, while sciatica nerve revealed that the nerve cells of the diabetic control rats showed marked degenerations. However, the treatment with coenzyme Q10, metformin or combination of both showed a significant increase in tissue regeneration capacity. In contrast, co-administration of coenzyme Q10 and metformin showed more tissue regeneration capacity when compared to diabetic control group as well as mono-therapy (coenzyme Q10 or metformin) (Figure 32).

**Fig. 32:** Light microscopy of sciatica nerve from rats (A) Normal control group, (B) Diabetic control group, (C) Coenzyme Q10 (D) Metformin (E) Coenzyme Q10 + Metformin.
4. Results

SET II

4.3. Studies on Nephropathy

4.3.1. Effect of coenzyme Q10, sitagliptin or concomitant administration on body weight and kidney weight

The body weight of the diabetic rats showed a significant decrease (P < 0.001) after the administration of STZ-nicotinamide as compared to normal control rats. The treatment with coenzyme Q10 or sitagliptin or coenzyme Q10 + sitagliptin did not show any significant reduction in the body weight as compared with diabetic control rats (Table 3).

There was a significant (P < 0.001) increase in kidney weight after 6th week in diabetic control rats as compared to normal control rats, while the treatment with coenzyme Q10 or sitagliptin showed a significant (P < 0.01) reduction in kidney weight as compared to diabetic control rats. The treatment with coenzyme Q10 and sitagliptin showed a significant (P < 0.001) reduction in kidney weight as compared to diabetic control rats. Moreover, co-administration of coenzyme Q10 with sitagliptin showed more beneficial effect in reducing kidney weight than when coenzyme Q10 administered singly (Table 3).

**Table 3: Effect of coenzyme Q10, sitagliptin or combination of both on body weight and kidney weight.**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial body weight (g)</th>
<th>Final body weight (g)</th>
<th>Kidney weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (a)</td>
<td>235.0 ± 5.28</td>
<td>255.0 ± 5.21</td>
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<tr>
<td>Diabetic control (b)</td>
<td>271.7 ± 9.14</td>
<td>186.7 ± 11.5###</td>
<td>1.18 ± 0.06###</td>
</tr>
<tr>
<td>Coenzyme Q10 (10 mg/kg) (c)</td>
<td>225.0 ± 8.76</td>
<td>196.7 ± 9.28</td>
<td>0.94 ± 0.02**</td>
</tr>
<tr>
<td>Sitagliptin (10 mg/kg) (d)</td>
<td>228.0 ± 8.64</td>
<td>214.0 ± 8.55</td>
<td>0.81 ± 0.02**</td>
</tr>
<tr>
<td>Coenzyme Q10 + Sitagliptin (e)</td>
<td>231.8 ± 9.19</td>
<td>222.7 ± 9.31</td>
<td>0.74 ± 0.01****+</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM; n=6

a vs b, ### P < 0.001; b vs c, b vs d and b vs e, *** P < 0.001; c vs e, +P < 0.01.
4.3.2. Effect of coenzyme Q10, sitagliptin or combination of both on urine volume

In diabetic control group, urine volume was significantly (P < 0.001) increased when compared to the normal control rats, while the treatment with coenzyme Q10 showed a significant (P < 0.05) reduction in urine volume as compared to diabetic rats. When diabetic rats treated with sitagliptin or coenzyme Q10 + sitagliptin there was a significant (P < 0.01; P < 0.001) reduction in urine volume as compared to diabetic control rats. However, co-administration of both showed a greater (P < 0.001; P < 0.01) reduction in urine volume than that of mono-therapy (coenzyme Q10 or sitagliptin) (Figure 33).

![Urine volume chart]

Fig. 33: Effect of coenzyme Q10, sitagliptin or combination of both on urine volume

Values are expressed as mean ± SEM; n=6
a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, * P < 0.05, ** P < 0.01, *** P < 0.001;
c vs. e, +++P < 0.001;
d vs. e, $$P < 0.01.
4. Results

4.3.3. Effect of coenzyme Q10, sitagliptin or combination of both on urinary protein

Six week post STZ-nicotinamide injection caused a significant (P < 0.001) increase urinary protein of diabetic rats as compared to normal control rats. The treatment with coenzyme Q10, sitagliptin or coenzyme Q10 + sitagliptin showed a significant (P < 0.01 or P < 0.001 or P < 0.001) reduction in urinary protein when compared to diabetic control rats. However, co-administration of both showed a greater (P < 0.001; P < 0.05) reduction in urine volume than that of mono-therapy (coenzyme Q10 or sitagliptin) (Figure 34).

**Fig. 34: Effect of coenzyme Q10, sitagliptin or combination of both on urinary protein**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
c vs. e, +++P < 0.001;
d vs. e, $P < 0.05.
4. Results

4.3.4. Effect of coenzyme Q10, sitagliptin or combination of both on glycated hemoglobin level

In the diabetic control rats, glycated hemoglobin levels were significantly (\(P < 0.001\)) increased when compared to normal control rats. The diabetic rats treated with coenzyme Q10 showed a significant (\(P < 0.05\)) reduction in glycated hemoglobin level as compared to diabetic control rats. However, the treatment with sitagliptin or coenzyme Q10 + sitagliptin showed a significant (\(P < 0.001\)) reduction in glycated hemoglobin levels as compared to diabetic control rats. Moreover, co-administration of coenzyme Q10 with sitagliptin showed more beneficial effect in reducing glycated hemoglobin (\(P < 0.001; P < 0.01\)) levels than when coenzyme Q10 or sitagliptin administered singly (Figure 35).

**Fig. 35: Effect of coenzyme Q10, sitagliptin or combination of both on glycated hemoglobin level**

Values are expressed as mean ± SEM; n=6

a vs. b, ### \(P < 0.001\);
b vs. c, b vs. d and b vs. e, *\(P < 0.05\), ***\(P < 0.001\);
c vs. e, +++ \(P < 0.001\); d vs. e, $$P < 0.01.$$
4.3.5. *Effect of coenzyme Q10, sitagliptin or combination of both on serum creatinine*

STZ-nicotinamide injection caused a marked reduction in renal function characterized by significant ($P < 0.001$) increase in serum creatinine levels as compared to normal control rats. Thus, these data indicate that a single i.p injection of STZ-nicotinamide impairs kidney functions. Treatment with coenzyme Q10, sitagliptin or coenzyme Q10 + sitagliptin showed a significant ($P < 0.01; P < 0.001$ and $P < 0.001$) reduction in serum creatinine levels as compared to diabetic control rats. In contrast, the combination of coenzyme Q10 and sitagliptin showed more beneficial effect in reducing serum creatinine ($P < 0.001; P < 0.05$) levels than that of mono-therapy (coenzyme Q10 or sitagliptin) alone (Figure 36).

![Serum creatinine](image.png)

**Fig. 36: Effect of coenzyme Q10, sitagliptin or combination of both on serum creatinine**

Values are expressed as mean ± SEM; n=6

a vs. b, ### $P < 0.001$;

b vs. c, b vs. d and b vs. e, ** $P < 0.01$, $$$ P < 0.001$;

c vs. e, +++ $P < 0.001$;

d vs. e, $\$ P < 0.05$. 
4.3.6. Effect of coenzyme Q10, sitagliptin or combination of both on serum urea

STZ-nicotinamide injection caused a marked reduction in renal function characterized by significant ($P < 0.001$) increase in serum urea levels as compared to normal control rats. The treatment with coenzyme Q10, sitagliptin or coenzyme Q10 + sitagliptin showed a significant ($P < 0.01; P < 0.01$ and $P < 0.001$) reduction in urea levels as compared to diabetic control rats, respectively. In addition, concomitant administration of coenzyme Q10 and sitagliptin showed more beneficial ($P < 0.01$) effect in reducing serum urea levels than when coenzyme Q10 or sitagliptin given alone (Figure 37).

**Serum urea**

![](image)

**Fig. 37:** Effect of coenzyme Q10, sitagliptin or combination of both on serum urea

Values are expressed as mean ± SEM; n=6

a vs. b, ### $P < 0.001$;
b vs. c, b vs. d and b vs. e, ### $P < 0.01$, ### $P < 0.001$;
c vs. e, ++$P < 0.01$;
d vs. e, $$P < 0.01$. 

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4.3.7. Effect of coenzyme Q10, sitagliptin or combination of both on serum uric acid

STZ-nicotinamide injection caused a marked reduction in renal function characterized by significant ($P < 0.001$) increase in serum uric acid levels as compared to normal control rats. Treatment with coenzyme Q10, sitagliptin or coenzyme Q10 + sitagliptin showed a significant ($P < 0.01; P < 0.001$ and $P < 0.001$) decreases in uric acid levels as compared to diabetic control rats, respectively. In addition, concomitant administration of coenzyme Q10 and sitagliptin showed more beneficial effect in reducing serum uric acid ($P < 0.001; P < 0.05$) levels than when coenzyme Q10 or sitagliptin given alone (Figure 38).

![Serum uric acid graph](image)

**Fig. 38:** Effect of coenzyme Q10, sitagliptin or combination of both on serum uric acid

Values are expressed as mean ± SEM; n=6

- a vs. b, $$$P < 0.001$;
- b vs. c, b vs. d and b vs. e, $**P < 0.01, ***P < 0.001$;
- c vs. e, +++$P < 0.001$;
- d vs. e, $^5P < 0.05$. 

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4. Results

4.3.8. Effect of coenzyme Q10, sitagliptin or combination of both on total cholesterol

STZ-nicotinamide injection showed a significant (P < 0.001) increase in serum total cholesterol levels as compared to normal control rats. Treatment with coenzyme Q10 showed a significant (P < 0.05) reduction in serum total cholesterol levels as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + sitagliptin showed a more significant (P < 0.01) reduction in serum total cholesterol levels as compared to diabetic control rats, while the sitagliptin treated rats did not show a significant difference in serum total cholesterol levels as compared to diabetic control rats (Figure 39).

Fig. 39: Effect of coenzyme Q10, sitagliptin or combination of both on total cholesterol

Values are expressed as mean ± SEM; n=6
a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01
4. Results

4.3.9. Effect of coenzyme Q10, sitagliptin or combination of both on serum triglyceride

STZ-nicotinamide injection showed a significant (P < 0.001) increase in serum triglyceride levels as compared to normal control rats. Treatment with coenzyme Q10 or sitagliptin showed a significant (P < 0.05; P < 0.01) reduction in serum triglyceride levels as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + sitagliptin showed more significant (P < 0.001) reduction in serum triglyceride levels as compared to diabetic control rats. There was not any significant improvement on serum triglyceride in combination therapy of both (coenzyme Q10 and sitagliptin) than that of mono-therapy (coenzyme Q10 or sitagliptin) (Figure 40).

![Diagram showing effect of coenzyme Q10, sitagliptin or combination of both on serum triglyceride](image)

Fig. 40: Effect of coenzyme Q10, sitagliptin or combination of both on serum triglyceride

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01, ***P < 0.01.
4. Results

4.3.10. **Effect of coenzyme Q10, sitagliptin or combination of both on HDL-C**

STZ-nicotinamide injection showed a significant (P < 0.001) decrease in HDL-C levels as compared to normal control rats. Treatment with coenzyme Q10 showed a significant (P < 0.05) increase in HDL-C levels as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + sitagliptin showed a more significant (P < 0.01) rise in HDL-C levels as compared to diabetic control rats, while the sitagliptin treated rats did not show a significant difference in serum HDL-C levels as compared to diabetic control rats (Figure 41).

**Fig. 41**: Effect of coenzyme Q10, sitagliptin or combination of both on HDL-C

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01.
4. Results

4.3.11. Effect of coenzyme Q10, sitagliptin or combination of both on malondialdehyde in renal tissue

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly $(P < 0.001)$ increased in renal tissue of diabetic control rats as compared to non diabetic rats after six weeks of study. The treatment of diabetic rats with coenzyme Q10 or sitagliptin or coenzyme Q10 + sitagliptin showed a significant $(P < 0.01; P < 0.05$ and $P < 0.001)$ decrease in the levels of MDA as compared to diabetic control rats. There was more significant $(P < 0.05)$ alteration in MDA levels when coenzyme Q10 and sitagliptin were given together than that of mono-therapy (sitagliptin) (Figure 42).

![Malondialdehyde](image)

**Fig. 42:** Effect of coenzyme Q10, sitagliptin or combination of both on malondialdehyde in renal tissue

Values are expressed as mean ± SEM; n=6

- a vs. b, ### $P < 0.001$;
- b vs. c, b vs. d and b vs. e, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$;
- d vs. e, $^5P < 0.05$. 
4.3.12. Effect of coenzyme Q10, sitagliptin or combination of both on GSH levels in renal tissue

In diabetic control rats, there was significantly (P < 0.001) decreased in the levels of GSH, an endogenous antioxidant in renal tissue as compared to normal control group. The treatment of diabetic rats with coenzyme Q10 or coenzyme Q10 + sitagliptin showed a significant (P < 0.001) decrease in the levels of GSH as compared to diabetic control rats, while sitagliptin treated rats showed a significant (P < 0.05) increase in the levels of GSH as compared to diabetic control rats. However, co-administration of both showed a significant (P < 0.05) alteration in GSH levels than when sitagliptin was given alone (Figure 43).

Fig. 43: Effect of coenzyme Q10, sitagliptin or combination of both on GSH levels in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, *P < 0.05, ***P < 0.001;
d vs. e, $P < 0.05.
4. Results

4.3.13. Effect of coenzyme Q10, sitagliptin or combination of both on SOD in renal tissue

There was a significant (P < 0.001) decrease in antiperoxidative enzymes (SOD) in renal tissue as compared to normal control group. While sitagliptin treated rats showed a significant (P < 0.05) increase in SOD activities as compared to diabetic control rats. Coenzyme Q10 or coenzyme Q10 + sitagliptin showed more significant (P < 0.001) increase in SOD activities as compared to diabetic control rats. There was more significant (P < 0.05) changes in SOD levels when coenzyme Q10 and sitagliptin were given together than that of mono-therapy (sitagliptin) (Figure 44).

![Superoxide dismutase](image)

Fig. 44: Effect of coenzyme Q10, sitagliptin or combination of both on SOD in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01, ***P < 0.001;

d vs. e, $P < 0.05.$
4. Results

4.3.14. Effect of coenzyme Q10, sitagliptin or combination of both on catalase in renal tissue

There was a significant (P < 0.001) decrease in the levels of catalase in renal tissue as compared to normal control group. The treatment of diabetic rats with coenzyme Q10 or coenzyme Q10 + sitagliptin showed a significant (P < 0.001) increase in catalase activities, while the sitagliptin treated rats showed a significant (P < 0.01) increase in catalase activities. There were more significant (P < 0.01) changes in catalase levels when coenzyme Q10 and sitagliptin were given together than when sitagliptin administered alone (Figure 45).

Fig. 45: Effect of coenzyme Q10, sitagliptin or combination of both on catalase in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, *** P < 0.001;
d vs. e, $$P < 0.01.
4.3.15. Effect of coenzyme Q10, sitagliptin or combination of both on TNF-α in renal tissue

Diabetic control rats showed a significant (P < 0.001) increase in inflammatory markers such as renal TNF-α level as compared to normal control rats. The treatment with coenzyme Q10 or sitagliptin or coenzyme Q10 + sitagliptin in STZ-nicotinamide treated rats showed a significant reduction in TNF-α (P < 0.001) levels in renal tissue when compared to diabetic control rats. However, treatment with coenzyme Q10 + sitagliptin showed more significant (P < 0.05) decrease in TNF-α level in renal tissue as compared to diabetic rats treated with sitagliptin or coenzyme Q10 alone. There was more beneficial effect in reducing TNF-α level when coenzyme Q10 and sitagliptin were given together than that of coenzyme Q10 or sitagliptin administered singly (Figure 46).

**Tumor necrotic factor-α**

![Graph showing the effect of coenzyme Q10, sitagliptin, or combination on TNF-α level in renal tissue](image)

*Fig. 46: Effect of coenzyme Q10, sitagliptin or combination of both on TNF-α level in renal tissue*

Values are expressed as mean ± SEM; n=6

- a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, * P < 0.05, ### P < 0.001;
- c vs. e, + P < 0.05; d vs. e, $ P < 0.05.
6.3.16. Effect of coenzyme Q10, sitagliptin or combination of both on TGF-β levels in renal tissue

Renal TGF-β level was significantly (P < 0.001) increased in diabetic control rats as compared to normal control rats. The treatment with coenzyme Q10 in STZ-nicotinamide treated rats showed a significant (P < 0.01) reduction in renal TGF-β when compared to diabetic control rats. However, treatment with sitagliptin or coenzyme Q10 + sitagliptin showed more significant (P < 0.001) decrease in renal TGF-β levels as compared to diabetic rats treated with sitagliptin or coenzyme Q10 alone (Figure 47).

![TGF-β Graph](image)

**Fig. 47:** Effect of coenzyme Q10, sitagliptin or combination of both on TGF-β levels in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, *P < 0.05, ***P < 0.001;
4. Results

4.3.17. Effect of coenzyme Q10, sitagliptin or combination of both on myeloperoxidase (MPO) activity in renal tissue

Diabetic control rats showed a significant (P < 0.001) increase in inflammatory markers such as renal MPO activity as compared to normal control rats. The treatment with coenzyme Q10 in STZ-nicotinamide treated rats showed a significant (P < 0.05) reduction in renal MPO activity when compared to diabetic control rats. However, treatment with sitagliptin or coenzyme Q10 + sitagliptin showed more significant (P < 0.001) decrease in renal MPO activity as compared to diabetic control rats. There was more significant reduction in renal MPO activity when coenzyme Q10 and sitagliptin were given together than that of coenzyme Q10 administered singly (Figure 48).

Myeloperoxidase

![Bar graph showing myeloperoxidase activity in different groups]

**Fig. 48:** Effect of coenzyme Q10, sitagliptin or combination of both on myeloperoxidase (MPO) activity in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.001;

c vs. e, ++P < 0.01.
4.3.18. Effect of coenzyme Q10, sitagliptin or combination of both on nitrite content in renal tissue

Nitrite content was significantly (P < 0.001) increased in renal tissue of diabetic rats as compared to normal control group. The coenzyme Q10 + sitagliptin treatment group showed more significant (P < 0.001) decrease renal nitrite content as compared to diabetic untreated group, while coenzyme Q10 alone or sitagliptin alone caused a significant (P < 0.01) decrease nitrite content in renal tissue as compared to diabetic rats, but this effect was much lesser than combination therapy (Figure 49).

![Graph showing nitrite content in renal tissue](image)

**Fig. 49: Effect of coenzyme Q10, sitagliptin or combination of both on nitrite content in renal tissue**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001.
4.3.19. **Histopathological Studies**

The architecture of the kidney was disturbed with diabetic control rats as compared to normal structural features of control animal. In the normal control group, the Histopathological examination of kidney tissue showed normal appearance of glomeruli and tubules. Renal tissue section of diabetic rats showed glomerulosclerosis ($), tubular vacuolization (*), interstitial fibrosis (+) and thickening of glomerular basement membrane (#). The treatment with coenzyme Q10 or sitagliptin showed mild glomerular necrosis, interstitial fibrosis, moderate tubular vacuolization, thickening of glomerular basement membrane. However, the treatment with concomitant administration of coenzyme Q10 with sitagliptin showed a mild glomerular fibrosis, tubular swelling and interstitial fibrosis with absence of glomerular necrosis [Fig. 50A-E].
Fig. 50: Light microscopy of kidney tissues from rats (HE stained kidney sections). (A) Control group, (B) Diabetic control group, (C) Coenzyme Q10 (D) Sitagliptin (E) Coenzyme Q10 + Sitagliptin.
4. Results

4.4. Studies on Neuropathy

4.4.1. Effect of coenzyme Q10, sitagliptin or combination of both on muscular grip strength

Measurement of muscular grip strength was used to evaluate diabetic neuropathy after streptozotocin-nicotinamide injection. In diabetic control group, muscular grip strength was significantly (P < 0.001) decreased as compared to normal control rats. The treatment of diabetic rats with coenzyme Q10 showed a significant (P < 0.01) improvement in the muscular grip strength as compared to diabetic control rats. However, the treatment with sitagliptin or coenzyme Q10 + sitagliptin showed more significant (P < 0.001) improvement in the muscular grip strength as compared to diabetic control rats. On the other hand, co-administration of coenzyme and sitagliptin showed a significant (P < 0.001; P < 0.05) increase in muscular grip strength than when coenzyme Q10 or sitagliptin administered singly (Figure 51).

![Muscular grip strength chart]

Fig. 51: Effect of coenzyme Q10, sitagliptin or combination of both on muscular grip strength

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, ** P < 0.01, *** P < 0.001;

c vs. e, +++ P < 0.001; d vs. e, $ P < 0.05.
4.4.2. Effect of coenzyme Q10, sitagliptin or combination of both on pain sensation (thermal pain)

The paw withdrawal response was measured by the Eddy’s hot plate. In diabetic rats, there was a significant ($P < 0.001$) increase in paw withdrawal response as compared to normal control rats showing significant nerve damage in diabetic animals. The paw withdrawal response of all treated rats on day 42 was significantly decreased as compared with the diabetic control group. The treatment of diabetic rats with coenzyme Q10 or sitagliptin or coenzyme Q10 + sitagliptin showed a significant ($P < 0.001$) decrease in paw withdrawal response as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + sitagliptin showed more significant ($P < 0.05$) decrease in paw withdrawal response than when coenzyme Q10 or sitagliptin administered singly (Figure 52).

Fig. 52: Effect of coenzyme Q10, sitagliptin or combination of both on pain sensation (thermal pain)
Values are expressed as mean ± SEM; n=6
a vs. b, ### $P < 0.001$;
b vs. c, b vs. d and b vs. e, ###$P < 0.001$;
c vs. e, +$P < 0.05$;
d vs. e, $^5P < 0.05$.  

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4.4.3. Effect of coenzyme Q10, sitagliptin or combination of both on pain sensation (tail flick)

In diabetic rats, there was a significant (P < 0.001) increase in tail flick response as compared to normal control rats. The tail flick response of all treated rats on d 42 was significantly decreased compared with the diabetic control group. The treatment of diabetic rats with coenzyme Q10 showed a significant (P < 0.01) decrease in tail flick response as compared to diabetic control rats. However, the treatment with sitagliptin or coenzyme Q10 + sitagliptin showed more significant (P < 0.001) decrease in tail flick response as compared to diabetic control rats. On the other hand, co-administration of coenzyme Q10 and sitagliptin showed a significant (P < 0.001; P < 0.05) decrease in tail flick response than when administered singly (coenzyme Q10 or sitagliptin) (Figure 53).

**Fig. 53:** Effect of coenzyme Q10, sitagliptin or combination of both on pain sensation (tail flick)

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;

b vs. e, +++ P < 0.001;

d vs. e, $P < 0.05.
4.4.4. *Effect of coenzyme Q10, sitagliptin or combination of both on malondialdehyde in sciatic nerve* 

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly (P < 0.001) increased in sciatic nerve of diabetic control rats as compared to non diabetic rats after six weeks of study. The treatment of diabetic rats with coenzyme Q10 or sitagliptin or coenzyme Q10 + sitagliptin showed a significant (P < 0.01; P < 0.05; P < 0.01) decrease in the levels of MDA as compared to diabetic control rats. However, co-administration of coenzyme and sitagliptin did not show any beneficial effect in reducing MDA than when administered singly (Figure 54).

![Bar chart showing Malondialdehyde levels across different groups](image)

**Fig. 54: Effect of coenzyme Q10, sitagliptin or combination of both on malondialdehyde in sciatic nerve**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01.
4.4.5. Effect of coenzyme Q10, sitagliptin or combination of both on SOD activity in sciatic nerve

There was a significant (P < 0.001) decrease in the antiperoxidative enzymes (SOD) in sciatic nerve as compared to normal control group. The treatment of diabetic rats with coenzyme Q10 or sitagliptin showed a significant (P < 0.01) increase in SOD activities as compared to diabetic control rats, respectively. However, coenzyme Q10 + sitagliptin showed more significant (P < 0.001) increase in SOD activities as compared to diabetic control rats. On the other hand, co-administration of coenzyme Q10 and sitagliptin showed a significant (P < 0.05) increase in SOD activities than when administered singly (sitagliptin) (Figure 55).

![Superoxide dismutase graph](image)

**Fig. 55: Effect of coenzyme Q10, sitagliptin or combination of both on SOD activity in sciatic nerve**

Values are expressed as mean ± SEM; n=6
a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
d vs. e, $P < 0.05.
4. Results

4.4.6. Effect of coenzyme Q10, sitagliptin or combination of both on GSH level in sciatic nerve

There was a significant (P < 0.001) decrease in the levels of GSH, an endogenous antioxidant in sciatic nerve as compared to normal control group. The treatment of diabetic rats with coenzyme Q10 or coenzyme Q10 + sitagliptin showed a significant (P < 0.001) increase in the levels of GSH as compared to diabetic control rats, respectively. The treatment with sitagliptin showed a significant (P < 0.05) increase in the levels of GSH as compared to diabetic control rats. However, the treatment with coenzyme Q10 + sitagliptin showed a significant (P < 0.05) increase in the levels of GSH levels than that of mono-therapy (sitagliptin), but co-administration of both did not show any significant difference in GSH level in sciatic nerve as compared to coenzyme Q10 alone treatment (Figure 56).

![GSH graph](image-url)

**Fig. 56:** Effect of coenzyme Q10, sitagliptin or combination of both on GSH level in sciatic nerve

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;

d vs. e, $P < 0.05.
4. Results

4.4.7. Histopathological studies of sciatic nerve

Histopathology of sciatic nerve in normal control rats showed normal structure, while sciatica nerve revealed that the nerve cells of the diabetic control rats showed marked degenerations. However, the treatment with coenzyme Q10, sitagliptin or combination of both showed a significant increase in tissue regeneration capacity. In contrast, co-administration of coenzyme Q10 and sitagliptin showed more tissue regeneration capacity when compared to diabetic control group as well as mono-therapy (coenzyme Q10 or sitagliptin) (Figure 57).

Fig. 57: Light microscopy of sciatica nerve from rats (A) Normal control group, (B) Diabetic control group, (C) Coenzyme Q10 (D) Sitagliptin (E) Coenzyme Q10 + Sitagliptin
4. Results

SET III

4.5. Studies on Nephropathy

4.5.1. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on body weight and kidney weight

The end of experiment, body weight of the diabetic rats showed a significant decrease after the administration of STZ-nicotinamide. The treatment with coenzyme Q10 + metformin or coenzyme Q10 + sitagliptin or coenzyme Q10+ metformin + sitagliptin did not show any significant reduction in the body weight as compared with diabetic control rats (Table 4).

There was a significant increase in kidney weight after 6th week in diabetic control rats, while the treatment with coenzyme Q10 + metformin or coenzyme Q10 + sitagliptin or coenzyme Q10+ metformin + sitagliptin showed a significant (P < 0.001) reduction in kidney weight as compared to diabetic control rats. Moreover, co-administration of coenzyme Q10 with metformin and sitagliptin showed more beneficial effect in reducing kidney weight than when coenzyme Q10 + metformin or coenzyme Q10 + sitagliptin administered together (Table 4).

Table 4: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on body weight and kidney weight.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial body weight (g)</th>
<th>Final body weight (g)</th>
<th>Kidney weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic control (a)</td>
<td>271.7 ± 9.14</td>
<td>186.7 ± 11.5***</td>
<td>1.18 ± 0.06***</td>
</tr>
<tr>
<td>Coenzyme Q10 + Metformin (b)</td>
<td>229.7 ± 12.09</td>
<td>212.7 ± 10.38</td>
<td>0.80 ± 0.02***</td>
</tr>
<tr>
<td>Coenzyme Q10 + Sitagliptin (c)</td>
<td>231.8 ± 9.19</td>
<td>222.7 ± 9.31</td>
<td>0.74 ± 0.01***</td>
</tr>
<tr>
<td>Coenzyme Q10 + Met + Sita (d)</td>
<td>235.7 ± 11.16</td>
<td>242.7 ± 15.31</td>
<td>0.71 ± 0.01***</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM; n=6

a vs b, ### P < 0.001;  b vs c, b vs d and b vs e, ***P < 0.001
4. Results

4.5.2. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on urine volume

When diabetic rats treated with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin, there was a significant (P < 0.001) reduction in urine volume as compared to diabetic control rats. However, coenzyme Q10 in combination with metformin and sitagliptin showed a greater (P < 0.001; P < 0.01) reduction in urine volume than that of co-administration of coenzyme Q10 with metformin or sitagliptin (Figure 58).

![Urine volume graph](image)

**Fig. 58**: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on urine volume

Values are expressed as mean ± SEM; n=6

a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &&& P < 0.001;
c vs. d, @@ P < 0.01.
4. Results

4.5.3. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on urinary protein

The treatment of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.001) reduction in urinary protein as compared to diabetic control rats. However, combination of coenzyme Q10 with metformin and sitagliptin showed a greater (P < 0.001) reduction in urinary protein than when coenzyme Q10 with metformin or sitagliptin was given together (Figure 59).

![Urinary Protein](image)

**Fig. 59: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on urinary protein**

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &&&P < 0.001;
c vs. d, @@@P < 0.001.
4. Results

4.5.4. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on glycated hemoglobin level

Diabetic rats treated with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.001) reduction in glycated hemoglobin as compared to diabetic control rats. However, coenzyme Q10 in combination with metformin and sitagliptin showed a greater (P < 0.05; P < 0.01) reduction in glycated hemoglobin than that of co-administration of coenzyme Q10 with metformin or sitagliptin (Figure 60).

Fig. 60: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on glycated hemoglobin level

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &P < 0.05;
c vs. d, @@P < 0.01.
4. Results

4.5.5. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on serum creatinine

Treatment with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.001) decrease in serum creatinine levels as compared to diabetic control rats. In contrast, coenzyme Q10 in combination with metformin and sitagliptin showed more beneficial effect in reducing serum creatinine (P < 0.01) levels than that of co-administration of coenzyme Q10 and sitagliptin (Figure 61).

![Serum creatinine graph]

**Fig. 61: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on serum creatinine**

Values are expressed as mean ± SEM; n=6

a vs. b, a vs. c and a vs. d, ***P < 0.001;

c vs. d, @@P < 0.01.
4. Results

4.5.6. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on serum urea

Serum urea was significantly (P < 0.001) decreased when diabetic rats treated with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin as compared to diabetic control rats. On the other hand, concomitant administration of coenzyme Q10, metformin and sitagliptin showed more beneficial (P < 0.05) effect in reducing serum urea levels than when coenzyme Q10 in combination with metformin or sitagliptin was given together (Figure 62).

![Serum urea graph]

Fig. 62: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on serum urea

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &P < 0.05;
c vs. d, @P < 0.05.
4.5.7. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on serum uric acid

The treatment with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.001) decrease in uric acid levels as compared to diabetic control rats. Moreover, coenzyme Q10 in combination with metformin and sitagliptin showed a greater (P < 0.05) effect in reducing serum uric acid levels than that of coenzyme Q10 given with sitagliptin together (Figure 63).

![Serum uric acid graph]

**Fig. 63:** Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on serum uric acid

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
c vs. d, @P < 0.05.
4.5.8. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on total cholesterol

When diabetic rats treated with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.05; P < 0.01; P < 0.01) reduction in serum total cholesterol levels as compared to diabetic control rats, respectively. Moreover, coenzyme Q10 in combination with metformin and sitagliptin did not show any significant reduction in total cholesterol levels than when coenzyme Q10 administered with metformin or sitagliptin together (Figure 64).

![Total cholesterol graph](image)

Fig. 64: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on total cholesterol

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
4.5.9. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on serum triglyceride

When diabetic rats treated with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.01; P < 0.001; P < 0.001) reduction in serum triglyceride levels as compared to diabetic control rats, respectively. On the other hand, coenzyme Q10 in combination with metformin and sitagliptin did not show any significant reduction in serum triglyceride levels than when coenzyme Q10 administered with metformin or sitagliptin together (Figure 65).

Fig. 65: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on serum triglyceride

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, **P < 0.01, ***P < 0.001;
4.5.10. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on HDL-C

The treatment with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant ($P < 0.01$; $P < 0.01$; $P < 0.001$) increases in HDL-C levels as compared to diabetic control rats, respectively. Moreover, coenzyme Q10 in combination with metformin and sitagliptin did not show any significant difference in HDL-C levels than when coenzyme Q10 administered with metformin or sitagliptin together (Figure 66).

![HDL-C Graph](image)

**Fig. 66:** Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on HDL-C

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, $**P < 0.01$, $***P < 0.001$;
4. Results

4.5.11. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on malondialdehyde in renal tissue

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly (P < 0.001) decreased in renal tissue of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin treated rats as compared to diabetic control rats after six weeks of study. The treatment of diabetic rats with coenzyme Q10 in combination with metformin and sitagliptin showed a significant (P < 0.05; P < 0.01) reduction in the levels of MDA as compared to coenzyme Q10 in combination with metformin or sitagliptin was given together (Figure 67).

Fig. 67: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin malondialdehyde in renal tissue

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &P < 0.05;
c vs. d, @@P < 0.01.
4. Results

4.5.12. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on GSH levels in renal tissue

Coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin treated showed a significant (P < 0.001) increase in the levels of GSH as compared to diabetic control rats. However, co-administration of coenzyme Q10 with metformin and sitagliptin showed a significant (P < 0.01; P < 0.05) alteration in GSH levels than when coenzyme Q10 in combination with metformin or sitagliptin was given together (Figure 68).

![Graph showing GSH levels](image)

**Fig. 68**: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on GSH levels in renal tissue

Values are expressed as mean ± SEM; n=6
- a vs. b, a vs. c and a vs. d, ***P < 0.001;
- b vs. d, &&P < 0.01;
- c vs. d, @P < 0.05.
4. Results

4.5.13. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on SOD in renal tissue

There was a significant (P < 0.001) increase in renal SOD levels of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin treated rats as compared to diabetic control group. The treatment of diabetic rats with coenzyme Q10 in combination with metformin and sitagliptin showed a significant (P < 0.01; P < 0.05) increase in the levels of SOD than when concomitant administration of coenzyme Q10 with metformin or sitagliptin (Figure 69).

**Fig. 69:** Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on SOD in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, a vs. c and a vs. d, **P < 0.001;**

b vs. d, &&P < 0.01;

c vs. d, @P < 0.05.
4. Results

4.5.14. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on catalase in renal tissue

There was a significant (P < 0.001) increase in renal catalase activities of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin treated rats as compared to diabetic control group. The treatment of diabetic rats with coenzyme Q10 in combination with metformin and sitagliptin showed a significant (P < 0.05) increase in renal catalase activities than when concomitant administration of coenzyme Q10 with metformin or sitagliptin (Figure 70).

![Catalase Graph]

Fig. 70: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on catalase in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &P < 0.05;
c vs. d, @P < 0.05.
4. Results

4.5.15. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on TNF-α in renal tissue

There was a significant (P < 0.001) decrease in renal TNF-α level of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin treated rats as compared to diabetic control group. The treatment of diabetic rats with coenzyme Q10 in combination with metformin and sitagliptin showed a significant (P < 0.05) decrease in renal TNF-α level than when concomitant administration of coenzyme Q10 with metformin or sitagliptin together (Figure 71).

![Tumor necrotic factor-α](image)

**Fig. 71**: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on TNF-α level in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &P < 0.05;
c vs. d, @P < 0.05.
4. Results

4.5.16. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on TGF-β levels in renal tissue

Renal TGF-β level was significantly (P < 0.001) decreased in coenzyme Q10 given with metformin or sitagliptin or metformin and sitagliptin as compared to diabetic control rats. The treatment with coenzyme Q10 in combination with metformin and sitagliptin in STZ-nicotinamide treated rats showed a significant (P < 0.01; P < 0.05) reduction in renal TGF-β levels as compared to diabetic rats treated with coenzyme Q10 and metformin or sitagliptin was given together (Figure 72).

**Fig. 72:** Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on TGF-β levels in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &&P < 0.01;
c vs. d, @P < 0.05.
4. Results

4.5.17. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on myeloperoxidase (MPO) activity in renal tissue

Diabetic control rats treated with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.001) decrease in inflammatory markers such as renal MPO activity as compared to diabetic control rats. However, coenzyme Q10 in combination with metformin and sitagliptin showed more significant (P < 0.01) decrease in renal MPO activity than when concomitant administration of coenzyme Q10 with metformin together (Figure 73).

Fig. 73: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on myeloperoxidase (MPO) activity in renal tissue

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &&P < 0.01.
4. Results

4.5.18. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on nitrite content in renal tissue

The coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin treatment group showed a significant (P < 0.001) decrease renal nitrite content as compared to diabetic untreated group, while coenzyme Q10 was given with metformin and sitagliptin caused a significant (P < 0.001) decrease nitrite content in renal tissue as compared to diabetic rats treated with coenzyme Q10 and metformin or sitagliptin was given together (Figure 74).

![Graph showing NO levels](image)

Fig. 74: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on nitrite content in renal tissue

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &&&P < 0.001;
c vs. d, @@@P < 0.001.
4.5.19. Histopathological Studies

The architecture of the kidney was disturbed with diabetic control rats. Renal tissue section of diabetic rats showed glomerulosclerosis ($), tubular vacuolization (*), interstitial fibrosis (+) and thickening of glomerular basement membrane (#). However, the treatment with concomitant administration of coenzyme Q10 with metformin or sitagliptin showed a mild glomerular fibrosis, tubular swelling and interstitial fibrosis with absence of glomerular necrosis. In contrast, the treatment with concomitant administration of coenzyme Q10 with metformin and sitagliptin group, the histopathological examination of kidney tissue showed normal appearance of glomeruli and tubules (Fig. 75A-D).

![Light microscopy of kidney tissues from rats (HE stained kidney sections). (A) Diabetic control group (B) Coenzyme Q10 + metformin (C) Coenzyme Q10 + sitagliptin (D) Coenzyme Q10 + metformin + sitagliptin.](image)
4. Results

4.6. Studies on Neuropathy

4.6.1. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on muscular grip strength

When diabetic rats treated with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin, there was significantly (P < 0.001) increased in muscular grip strength as compared to diabetic control rats. The treatment with coenzyme Q10 in combination with metformin and sitagliptin in STZ-nicotinamide treated rats showed a significant (P < 0.001) increase in muscular grip strength as compared to diabetic rats treated with coenzyme Q10 and metformin or sitagliptin was given together (Figure 76).

![Muscle grip graph]

**Fig. 76: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on muscular grip strength**

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &&&P < 0.001;
c vs. d, @@@P < 0.001.
4. Results

4.6.2. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on pain sensation (thermal pain)

The paw withdrawal response of all treated rats on day 42 was significantly decreased as compared with the diabetic control group. The treatment of diabetic rats with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.001) decrease in paw withdrawal response as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 in combination with metformin and sitagliptin showed more significant (P < 0.05) decrease in paw withdrawal response than when co-administration of coenzyme Q10 with metformin or sitagliptin (Figure 77).

Fig. 77: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on pain sensation (thermal pain)

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &P < 0.05;
c vs. d, @P < 0.05.
4. Results

4.6.3. **Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on pain sensation (tail flick)**

The tail flick response of all treated rats on d 42 was significantly decreased compared with the diabetic control group. The treatment of diabetic rats with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.001) decrease in tail flick response as compared to diabetic control rats. However, the treatment with coenzyme Q10 in combination with metformin and sitagliptin showed more significant (P < 0.05) decrease in tail flick response than when co-administration of coenzyme Q10 with metformin (Figure 78).

**Tail flick response**

**Fig. 78:** Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on pain sensation (tail flick)

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &P < 0.01.
4.6.4. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on malondialdehyde in sciatic nerve

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly (P < 0.001) decreased in sciatic nerve of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin as compared to diabetic rats after six weeks of study. The treatment of diabetic rats with coenzyme Q10 in combination with metformin and sitagliptin showed a significant (P < 0.05; P < 0.001) reduction in MDA levels than when co-administration of coenzyme with metformin or sitagliptin (Figure 79).

![Graph showing the effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on malondialdehyde in sciatic nerve](image)

**Fig. 79:** Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on malondialdehyde in sciatic nerve

Values are expressed as mean ± SEM; n=6

a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &P < 0.05;
c vs. d, @@@P < 0.001.
4.6.5. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on SOD activity in sciatic nerve

The treatment of diabetic rats with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant (P < 0.001) increase in SOD activities as compared to diabetic control rats. However, coenzyme Q10 metformin + sitagliptin treated rats showed did not show any significant difference in SOD activities than when co-administration of coenzyme with metformin or sitagliptin (Figure 80).

![Superoxide dismutase graph]

Fig. 80: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on SOD activity in sciatic nerve

Values are expressed as mean ± SEM; n=6
a vs. b, a vs. c and a vs. d, ***P < 0.001;
4. Results

4.6.6. Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on GSH level in sciatic nerve

There was a significant (P < 0.001) increase in the levels of GSH, an endogenous antioxidant in sciatic nerve of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin as compared to diabetic control group. In addition, the treatment of diabetic rats with coenzyme Q10 in combination with metformin and sitagliptin showed a significant (P < 0.001) increase in GSH levels than when co-administration of coenzyme with metformin or sitagliptin (Figure 81).

![GSH levels comparison](image)

**Fig. 81: Effect of coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin on GSH level in sciatic nerve**

Values are expressed as mean ± SEM; n=6

a vs. b, a vs. c and a vs. d, ***P < 0.001;
b vs. d, &&&P < 0.001;
c vs. d, @@@P < 0.01.
4.6.7. Histopathological studies of sciatic nerve

Sciatica nerve revealed that the nerve cells of the diabetic control rats showed marked degenerations. However, the treatment with coenzyme Q10 in combination with metformin or sitagliptin or metformin and sitagliptin showed a significant increase in tissue regeneration capacity. In contrast, co-administration of coenzyme Q10 and metformin and sitagliptin showed more tissue regeneration capacity when co-administration of coenzyme with metformin or sitagliptin (Figure 82A-D).

**Fig. 82:** Light microscopy of sciatica nerve from rats (A) Diabetic control group, (B) Coenzyme Q10 + Metformin (C) Coenzyme Q10 + Sitagliptin (D) Coenzyme Q10 + Metformin +Sitagliptin
4. Results

SET IV

4.7. Studies on Nephropathy

4.7.1. Effect of coenzyme Q10, rosuvastatin or combination of both on body weight and kidney weight

The body weight of the diabetic rats showed a significant (P < 0.001) decrease after the administration of STZ-nicotinamide. The treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin did not show any reduction in the body weight as compared with diabetic control rats.

There was a significant (P < 0.001) increase in kidney weight after 6th week in diabetic control rats as compared to normal control rats, while the treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.01; P < 0.01; P < 0.01) reduction in kidney weight as compared to diabetic control rats (Table 5).

Table 5: Effect of coenzyme Q10, rosuvastatin or combination of both on body weight and kidney weight

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial body weight (g)</th>
<th>Final body weight (g)</th>
<th>Kidney weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (a)</td>
<td>235.0 ± 5.28</td>
<td>255.0 ± 5.21</td>
<td>0.59 ± 0.01</td>
</tr>
<tr>
<td>Diabetic control (b)</td>
<td>271.7 ± 9.14</td>
<td>186.7 ± 11.5***</td>
<td>1.18 ± 0.06***</td>
</tr>
<tr>
<td>Coenzyme Q10 (10 mg/kg) (c)</td>
<td>225.0 ± 8.76</td>
<td>196.7 ± 9.28</td>
<td>0.94 ± 0.02**</td>
</tr>
<tr>
<td>Rosuvastatin (10 mg/kg) (d)</td>
<td>234.0 ± 10.30</td>
<td>219.0 ± 11.65</td>
<td>0.87 ± 0.02**</td>
</tr>
<tr>
<td>Coenzyme Q10 + rosuvastatin (e)</td>
<td>239.7 ± 11.48</td>
<td>232.7 ± 8.49</td>
<td>0.82 ± 0.02***</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
4. Results

4.7.2. **Effect of coenzyme Q10, rosuvastatin or combination of both on urine volume**

In diabetic control group, urine volume was significantly (P < 0.001) increased when compared to the normal control rats. When diabetic rats treated with coenzyme Q10 or coenzyme Q10 + rosuvastatin showed a significant (P < 0.05; P < 0.01) reduction in urine volume as compared to diabetic control rats. However, rosuvastatin did not show any significant reduction in urine volume as compared to diabetic control rats. Combination of both did not show any significant reduction in urine volume as compared to coenzyme Q10 or rosuvastatin alone group (Figure 83).

![Urine volume graph](image)

**Fig. 83**: Effect of coenzyme Q10, rosuvastatin or combination of both on urine volume

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01.
4. Results

4.7.3. Effect of coenzyme Q10, rosuvastatin or combination of both on urinary protein

Six week post STZ-nicotinamide injection caused a significant (P < 0.001) increase urinary protein of diabetic rats as compared to normal control rats. The treatment with coenzyme Q10, rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.01; P < 0.01 and P < 0.001) reduction in urinary protein when compared to diabetic control rats. In contrast, co-administration of coenzyme and rosuvastatin showed a greater reduction (P < 0.001) in urine protein levels than when coenzyme Q10 or rosuvastatin administered singly (Figure 84).

![Urinary protein](image)

**Fig. 84: Effect of coenzyme Q10, rosuvastatin or combination of both on urinary protein**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
c vs. e, ^^^P < 0.001;
d vs. e, !!!P < 0.001.
4. Results

4.7.4. Effect of coenzyme Q10, rosuvastatin or combination of both on glycated hemoglobin level

In the diabetic control rats, glycated hemoglobin level were significantly (P < 0.001) increased when compared to normal control rats. The diabetic rats treated with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.05) reduction in glycated hemoglobin level as compared to diabetic control rats. Moreover, co-administration of coenzyme Q10 and rosuvastatin did not show any significant reduction in glycated hemoglobin level than when administered singly (coenzyme Q10 or rosuvastatin) (Figure 85).

![Glycated hemoglobin graph]

Fig. 85: Effect of coenzyme Q10, rosuvastatin or combination of both on glycated hemoglobin level

Values are expressed as mean ± SEM; n=6
a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, * P < 0.05;
4. Results

4.7.5. **Effect of coenzyme Q10, rosuvastatin or combination of both on serum creatinine**

STZ-nicotinamide injection caused a marked reduction in renal function, as characterized by significant ($P < 0.001$) increase in serum creatinine levels as compared to normal control rats. Thus, these data indicate that a single i.p injection of STZ-nicotinamide impairs kidney functions. Treatment with coenzyme Q10, rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant ($P < 0.01; P < 0.001$ and $P < 0.001$) reduction in serum creatinine levels as compared to diabetic control rats, respectively. Moreover, the combination of coenzyme Q10 and rosuvastatin showed more significant ($P < 0.001; P < 0.05$) reduction in serum creatinine levels than that of mono-therapy (coenzyme Q10 or rosuvastatin) (Figure 86).

![Serum creatinine](image)

**Fig. 86: Effect of coenzyme Q10, rosuvastatin or combination of both on serum creatinine**

Values are expressed as mean $\pm$ SEM; $n=6$

a vs. b, ### $P < 0.001$;  
b vs. c, b vs. d and b vs. e, **$P < 0.01$, ***$P < 0.001$;  
c vs. e, ^^^$P < 0.001$; d vs. e, ¹$P < 0.05$. 

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4. Results

4.7.6. Effect of coenzyme Q10, rosuvastatin or combination of both on serum urea

STZ-nicotinamide injection caused a significant (P < 0.001) increase in serum urea levels as compared to normal control rats. Treatment with coenzyme Q10, rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.01; P < 0.01 and P < 0.001) reduction in serum urea levels as compared to diabetic control rats, respectively. Moreover, there was a significant (P < 0.05) alteration of serum urea levels in combination therapy of both (coenzyme Q10 and rosuvastatin) than that of monotherapy (coenzyme Q10 or rosuvastatin) (Figure 87).

![Serum urea graph](image)

**Fig. 87: Effect of coenzyme Q10, rosuvastatin or combination of both on serum urea**

Values are expressed as mean ± SEM; n=6

- a vs. b, ###P < 0.001;
- b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
- c vs. e, *P < 0.05;
- d vs. e, †P < 0.05.
4.7.7. Effect of coenzyme Q10, rosuvastatin or combination of both on serum uric acid

STZ-nicotinamide injection caused a significant (P < 0.001) increase in serum uric acid levels as compared to normal control rats. The treatment with coenzyme Q10, rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.01; P < 0.01 and P < 0.001) decreases in uric acid levels as compared to diabetic control rats, respectively. Moreover, co-administration of coenzyme Q10 and rosuvastatin did not show a greater alteration in uric acid levels than when administered singly (coenzyme Q10 or rosuvastatin) (Figure 88).

![Serum uric acid graph]

**Fig. 88:** Effect of coenzyme Q10, rosuvastatin or combination of both on serum uric acid

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, *** P < 0.001;
4.7.8. Effect of coenzyme Q10, rosuvastatin or combination of both on total cholesterol

STZ-nicotinamide injection showed a significant (P < 0.001) increase in serum total cholesterol levels as compared to normal control rats. The treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.05) reduction in serum total cholesterol levels as compared to diabetic control rats. On the other hand, the co-administration of coenzyme Q10 + rosuvastatin treated rats did not show any significant alteration in total cholesterol level than when coenzyme Q10 or rosuvastatin administered singly (Figure 89).

**Fig. 89: Effect of coenzyme Q10, rosuvastatin or combination of both on total cholesterol**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, * P < 0.05.
4.7.9. Effect of coenzyme Q10, rosuvastatin or combination of both on serum triglyceride

STZ-nicotinamide injection showed a significant (P < 0.001) increase in serum triglyceride levels as compared to normal control rats. However, the treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.05; P < 0.001; P < 0.001) reduction in serum triglyceride levels as compared to diabetic control rats. Moreover, the coenzyme Q10 + rosuvastatin treated rats showed more significant (P < 0.001) reduction in serum triglyceride level than that of coenzyme Q10 administered alone (Figure 90).

![Triglyceride Chart]

**Fig. 90**: Effect of coenzyme Q10, rosuvastatin or combination of both on serum triglyceride

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, * P < 0.05; *** P < 0.001 .
c vs. e, ^^^ P < 0.001.
4. Results

4.7.10. Effect of coenzyme Q10, rosuvastatin or combination of both on HDL-C

Diabetic control rats showed a significant (P < 0.001) decrease in HDL-C levels as compared to normal control rats. In addition, the treatment with coenzyme Q10 showed a significant (P < 0.05) increase in HDL-C levels as compared to diabetic control rats, while the rosuvastatin or coenzyme Q10 + rosuvastatin treated rats showed a significant (P < 0.001) difference in HDL-C levels as compared to diabetic control rats. Moreover, concomitant administration of coenzyme Q10 + rosuvastatin showed a greater (P < 0.05) increase in HDL-C levels than that of mono-therapy (coenzyme Q10) (Figure 91).

![HDL-C](image)

**Fig. 91: Effect of coenzyme Q10, rosuvastatin or combination of both on HDL-C**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, *P < 0.05, ***P < 0.001;
c vs. e, ^P < 0.05.
4. Results

4.7.11. Effect of coenzyme Q10, rosvastatin or combination of both on malondialdehyde in renal tissue

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly (P < 0.001) increased in renal tissue of diabetic control rats as compared to non diabetic rats after six weeks of study. The treatment of diabetic rats with coenzyme Q10 or rosvastatin or coenzyme Q10 + rosvastatin showed a significant (P < 0.01; P < 0.01 and P < 0.001) decrease in the levels of MDA as compared to diabetic control rats. However, co-administration of coenzyme Q10 and rosvastatin showed a greater (P < 0.05) reduction in MDA levels than when rosvastatin administered singly, but combination of both did not show any significant difference in MDA levels than when coenzyme Q10 was given alone (Figure 92).

Fig. 92: Effect of coenzyme Q10, rosvastatin or combination of both on malondialdehyde level in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
d vs. e, 'P < 0.01
4.7.12. Effect of coenzyme Q10, rosuvastatin or combination of both on GSH level in renal tissue

There was a significant (P < 0.001) decrease in the levels of GSH, an endogenous antioxidant in renal tissue as compared to normal control group. In contrast, the treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.01; P < 0.01 and P < 0.001) increase in the levels of GSH as compared to diabetic control rats. However, co-administration of coenzyme and rosuvastatin showed a greater (P < 0.05) difference in GSH levels as compared to mono-therapy (rosuvastatin). Combination of both did not show any significant alteration in GSH levels than when coenzyme Q10 was given alone (Figure 93).

Fig. 93: Effect of coenzyme Q10, rosuvastatin or combination of both on GSH level in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001
d vs. e, †P < 0.05.
4.7.13. Effect of coenzyme Q10, rosuvastatin or combination of both on SOD activity in renal tissue

There was a significant (P < 0.001) decrease in the levels of antiperoxidative enzymes (SOD) in renal tissue as compared to normal control group. However, the treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.001; P < 0.05; P < 0.001) increase in SOD activities, while the co-administration of both showed more significant (P < 0.01) increase in SOD activities than that of rosuvastatin alone treatment (Figure 94).

![Superoxide dismutase](image_url)

**Fig. 94: Effect of coenzyme Q10, rosuvastatin or combination of both on SOD level in renal tissue**

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, * P < 0.05, *** P < 0.001;
d vs. e, ″ P < 0.01
4. Results

4.7.14. Effect of coenzyme Q10, rosuvastatin or combination of both on catalase activity in renal tissue

Diabetic rats showed a significant (P < 0.001) reduction in catalase activity as compared to normal control rats. However, the treatment of diabetic rats with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.001) increase in catalase activity as compared to diabetic control rats. On the other hand, the co-administration of coenzyme Q10 + rosuvastatin treated rats did not show any significant alteration in catalase activity than when coenzyme Q10 or rosuvastatin administered singly (Figure 95).

Fig. 95: Effect of coenzyme Q10, rosuvastatin or combination of both on catalase activity in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, *** P < 0.001;
4. Results

4.7.15. Effect of coenzyme Q10, rosuvastatin or combination of both on TNF-α level in renal tissue

Diabetic control rats showed a significant (P < 0.001) increase in inflammatory markers such as renal TNF-α level as compared to normal control rats. The treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin in STZ-nicotinamide treated rats showed a significant (P < 0.001) reduction in TNF-α level in renal tissue when compared to diabetic control rats. However, treatment with coenzyme Q10 + rosuvastatin showed more significant (P < 0.05) decrease in TNF-α level in renal tissue as compared to diabetic rats treated with coenzyme Q10 or rosuvastatin was administered alone (Figure 96).

![Tumor necrotic factor-α](image)

Fig. 96: Effect of coenzyme Q10, rosuvastatin or combination of both on TNF-α in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, ***P < 0.001;
c vs. e, ^P < 0.05; d vs. e, ¥P < 0.05.
4. Results

4.7.16. Effect of coenzyme Q10, rosuvastatin or combination of both on TGF-β level in renal tissue

Diabetic control rats showed a significant (P < 0.001) increase in inflammatory markers such as renal TGF-β as compared to normal control rats. The treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin in STZ-nicotinamide treated rats showed a significant (P < 0.01; P < 0.05; P < 0.001) reduction in TGF-β in renal tissue when compared to diabetic control rats. Moreover, co-administration of both did not show any significant changes in TGF-β level as compared to diabetic rats treated with rosuvastatin or coenzyme Q10 alone (Figure 97).

![TGF-β Chart]

Fig. 97: Effect of coenzyme Q10, rosuvastatin or combination of both on TGF-β level in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, *P < 0.05, **P < 0.01, ***P < 0.001
4. Results

4.7.17. Effect of coenzyme Q10, rosuvastatin or combination of both on myeloperoxidase (MPO) activity in renal tissue

Diabetic control rats showed a significant (P < 0.001) increase in MPO activity as compared to normal control rats. The treatment with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin in STZ-nicotinamide treated rats showed a significant (P < 0.05; P < 0.01; P < 0.001) reduction in MPO activity in renal tissue when compared to diabetic control rats. However, co-administration of both showed a significant (P < 0.05) changes in renal MPO activity as compared to diabetic rats treated with coenzyme Q10 alone (Figure 98).

![Myeloperoxidase](image)

Fig. 98: Effect of coenzyme Q10, rosuvastatin or combination of both on myeloperoxidase (MPO) activity in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c and b vs. e, *P < 0.05, **P < 0.01, ***P < 0.001
c vs. e, ^P < 0.05.
4. Results

4.7.18. Effect of coenzyme Q10, rosuvastatin or combination of both on nitrite content in renal tissue

Nitrite content was significantly (P < 0.001) increased in renal tissue of diabetic rats as compared to normal control group. The coenzyme Q10 + rosuvastatin treatment group showed more significant (P < 0.001) decrease renal nitrite content as compared to diabetic untreated group, while coenzyme Q10 alone or rosuvastatin alone caused a significant (P < 0.01) decrease in renal nitrite content as compared to diabetic rats, but this effect was much lesser than combination therapy. In contrast, concomitant administration coenzyme Q10 with rosuvastatin showed a significant (P < 0.05) reduction in renal nitrite content than that of mono-therapy (coenzyme Q10 or rosuvastatin) (Figure 99).

![Graph showing nitrite content in renal tissue](image)

Fig. 99: Effect of coenzyme Q10, rosuvastatin or combination of both on nitrite content in renal tissue

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
c vs. e, !P < 0.05; d vs. e, !P < 0.05
4. Results

4.7.19. Histopathological studies

In normal control group, kidney tissue showed normal appearance of glomeruli and tubules. Renal tissue section of diabetic rats showed glomerulosclerosis ($$), tubular vacuolization ($$), interstitial fibrosis ($$) and thickening of glomerular basement membrane ($$). The treatment with coenzyme Q10 or rosuvastatin showed mild to moderate glomerular necrosis, interstitial fibrosis, moderate tubular vacuolization, thickening of glomerular basement membrane. However, the treatment with concomitant administration of coenzyme Q10 with rosuvastatin showed a mild glomerular fibrosis, tubular swelling and interstitial fibrosis with absence of glomerular necrosis (Figure 100A-E).
4. Results

Fig. 100: Light microscopy of kidney tissues from rats (HE stained kidney sections). (A) Control group, (B) Diabetic control group, (C) Coenzyme Q10 (D) Rosuvastatin (E) Coenzyme Q10 + rosvastatin
4.8. Studies on Neuropathy

4.8.1. Effect of coenzyme Q10, rosuvastatin or combination of both on muscular grip strength

Measurement of muscular grip strength was used to evaluate diabetic neuropathy after streptozotocin-nicotinamide injection. In diabetic control group, muscular grip strength was significantly (P < 0.001) decreased as compared to normal control rats. The treatment of diabetic rats with coenzyme Q10 or rosuvastatin showed a significant (P < 0.01; P < 0.05) improve the muscular grip strength as compared to diabetic control rats. However, the treatment with coenzyme Q10 + rosuvastatin showed more significant (P < 0.001) increase in the muscular grip strength as compared to diabetic control rats. On the other hand, co-administration of coenzyme and rosuvastatin showed a significant (P < 0.05) increase in muscular grip strength than when coenzyme Q10 or rosuvastatin administered singly (Figure 101).

Fig. 101: Effect of coenzyme Q10, rosuvastatin or combination of both on muscular grip strength

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001; b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01, ***P < 0.001; c vs. e, ^P < 0.05; d vs. e, ′P < 0.05.
4.8.2. Effect of coenzyme Q10, rosuvastatin or combination of both on pain sensation (thermal pain)

In diabetic rats, there was a significant (P < 0.001) increase in paw withdrawal response as compared to normal control rats showing significant nerve damage in diabetic animals. The paw withdrawal response of all treated rats on day 42 was significantly decreased as compared with the diabetic control group. The treatment of diabetic rats with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.001; P < 0.01; P < 0.001) decrease in paw withdrawal response as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + rosuvastatin did not show any significant alterations in paw withdrawal response as compared to mono-therapy (coenzyme Q10 or rosuvastatin) (Figure 102).

Fig. 102: Effect of coenzyme Q10, rosuvastatin or combination of both on pain sensation (thermal pain)

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;

b vs. c, b vs. d and b vs. e, ** P < 0.01, *** P < 0.001;
4.8.3. Effect of coenzyme Q10, rosuvastatin or combination of both on pain sensation (tail flick)

In diabetic rats, there was a significant (P < 0.001) increase in tail flick response as compared to normal control rats. The tail flick response of all treated rats on d 42 was significantly decreased compared with the diabetic control group. The treatment of diabetic rats with coenzyme Q10 or rosuvastatin showed a significant (P < 0.01) decrease in tail flick response as compared to diabetic control rats. However, the treatment with coenzyme Q10 + rosuvastatin showed more significant (P < 0.001) decrease in tail flick response as compared to diabetic control rats. On the other hand, co-administration of coenzyme Q10 and rosuvastatin did not show any significant increase in tail flick response than when administered singly (coenzyme Q10 or rosuvastatin) (Figure 103).

![Graph showing tail flick response](image)

**Fig. 103: Effect of coenzyme Q10, rosuvastatin or combination of both on pain sensation (tail flick)**

Values are expressed as mean ± SEM; n=6

- a vs. b, ### P < 0.001;
- b vs. c, b vs. d and b vs. e, **P < 0.01, ***P < 0.001;
4. Results

4.8.4. Effect of coenzyme Q10, rosuvastatin or combination of both on malondialdehyde in sciatic nerve

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly (P < 0.001) increased in sciatic nerve of diabetic control rats as compared to non diabetic rats after six weeks of study. The treatment of diabetic rats with coenzyme Q10 or rosuvastatin showed a significant (P < 0.01) decrease in the levels of MDA as compared to diabetic control rats. Moreover, the treatment with coenzyme Q10 + rosuvastatin showed more significant (P < 0.001) reduction in the levels of MDA levels as compared to diabetic control rats. However, co-administration of coenzyme and rosuvastatin has more beneficial effect than when administered singly (Figure 104).

![Malondialdehyde Graph](image)

Fig. 104: Effect of coenzyme Q10, rosuvastatin or combination of both on malondialdehyde in sciatic nerve

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, ** P < 0.01, *** P < 0.001;
4.8.5. Effect of coenzyme Q10, rosuvastatin or combination of both on SOD activity in sciatic nerve

There was a significant (P < 0.001) decrease in the antiperoxidative enzymes (SOD) in sciatic nerve as compared to normal control group. The treatment of diabetic rats with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.001; P < 0.05; P < 0.001) increase in SOD activities as compared to diabetic control rats, respectively (Figure 105).

![Superoxide dismutase](image)

Fig. 105: Effect of coenzyme Q10, rosuvastatin or combination of both on SOD activity in sciatic nerve

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, *P < 0.05, **P < 0.01, *** P < 0.001;
4. Results

4.8.6. Effect of coenzyme Q10, rosuvastatin or combination of both on GSH level in sciatic nerve

There was a significant (P < 0.001) decrease in the levels of GSH, an endogenous antioxidant in sciatic nerve as compared to normal control group. The treatment of diabetic rats with coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin showed a significant (P < 0.001) increase in the levels of GSH as compared to diabetic control rats, respectively. However, the co-administration of both did not show any significant difference in GSH level in sciatic nerve as compared to coenzyme Q10 or rosuvastatin alone treatment (Figure 106).

Fig. 106: Effect of coenzyme Q10, rosuvastatin or combination of both on GSH level in sciatic nerve

Values are expressed as mean ± SEM; n=6

a vs. b, ### P < 0.001;
b vs. c, b vs. d and b vs. e, ###P < 0.001;
4. Results

4.8.7. Histopathological studies of sciatic nerve

Histopathology of sciatic nerve in normal control rats showed normal structure, while sciatica nerve revealed that the nerve cells of the diabetic control rats showed marked degenerations. However, the treatment with coenzyme Q10, rosuvastatin or combination of both showed a significant increase in tissue regeneration capacity. In contrast, co-administration of coenzyme Q10 and rosuvastatin showed more tissue regeneration capacity when compared to diabetic control group as well as mono-therapy (coenzyme Q10 or rosuvastatin) (Figure 107A-E).

Fig. 107: Light microscopy of sciatic nerve from rats (A) Control group, (B) Diabetic control group, (C) Coenzyme Q10 (D) Rosuvastatin (E) Coenzyme Q10 + Rosuvastatin.