EFFECT OF COENZYME Q10 ALONE AND ITS COMBINATION WITH ROSUVASTATIN ON STREPTOZOTOCIN-NICOTINAMIDE INDUCED DIABETIC NEUROPATHY IN RATS

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ABSTRACT

Objectives: This study was aimed to investigate the effect of coenzyme Q10 and its combination with rosuvastatin on STZ-nicotinamide induced diabetic neuropathy.

Methods: Diabetic neuropathy in rats were induced with streptozotocin-nicotinamide. The diabetic rats were treated with coenzyme Q10 or rosuvastatin or their combination. Various parameters like muscular gripp strength, paw withdrawal response, tail flick response and markers of oxidative stress such as malondialdehyde (MDA) level, superoxide dismutase (SOD) and reduced glutathione (GSH) in the sciatic nerve were measured. All treated animal was subjected to histopathological changes of sciatica nerve.

Results: In diabetic control group, muscular grip strength was significantly decreased and increased paw withdrawal response, tail flick response as compared to normal control rats. In addition, STZ-nicotinamide caused nerve cell damage with a higher MDA level, depletions of SOD and GSH level along with marked degeneration of the nerve cell. The treatment of diabetic rats with coenzyme Q10 or rosuvastatin or their combination ameliorate STZ-nicotinamide induced diabetic neuropathy. However, concomitant administration of both showed a better neuroprotective effect than coenzyme Q10 or rosuvastatin alone treatment.

Keywords: Diabetic neuropathy, Coenzyme Q10, Rosuvastatin, Muscular grip strength, Oxidative stress.

INTRODUCTION

Diabetic neuropathy is most common long-term complications of diabetes affecting 50% of the patient worldwide [1–3]. Diabetic nephropathy occurs as a result of damage to the nervous system due to persistent hyperglycemia can affect many parts of the body. The symptoms of diabetic neuropathy include pain, numbness, tingling. Neuropathic pain is usually considered to be one of the most upsetting complications affecting diabetic patients [4,5]. Current treatment for neuropathic pain includes antihypertensive (duloxetine, citalopram, venlafaxine), anticonvulsants (pregabalin, gabapentin, carbamazepine) and opioid and opioid-like drugs (tramadol, oxycodone). Pain relief with existing therapy is associated with many side effects [6-8]. It was previously reported that persistent and chronic hyperglycemia responsible for generation of reactive oxygen species and yield in the oxidative stress due to depletion of antioxidant defense system and damage to the peripheral neurons [9-11].

Coenzyme Q10 or ubiquinone has a potent antioxidant, scavenging free radicals and antidiabetic effect [12-14]. The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have pleiotropic effects on cerebrovascular, cardiovascular, and micro-vascular diseases independent of their cholesterol lowering effect [15].

Therefore, it was thought to combine antioxidant like coenzyme Q10 and rosuvastatin to study their neuroprotective effect in experimentally induced neuropathy. Hence, the present study was aimed to investigate the protective effect of coenzyme Q10 alone and its combination with rosuvastatin on STZ-nicotinamide induced diabetic neuropathy.

MATERIALS AND METHODS

Drugs and chemicals
Rosuvastatin and coenzyme Q10 were obtained from Zydus Cadila, Ahmedabad, India. Streptozotocin and nicotinamide were purchased from Himedia (Mumbai, India). All other chemicals and reagents used in the study were of analytical grade.

Experimental animals
The experimental protocol in the present study was approved by the Institutional Animal Ethics Committee (IAEC) and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The experiment was carried out on healthy adult Wistar rats weighing 200-250 g of either sex. Rats were housed in polypropylene cages, maintained under standardized condition (12-h light/dark cycle, 24°C, 35 to 60% humidity) and allowed free access to diet (Nav Maharashtra Oil Mills Pvt. Ltd., Pune) and purified drinking water ad libitum.

Induction of diabetic neuropathy
Type 2 diabetes was induced in overnight fasted adult albino Wistar rats (200-250g) by a single intraperitoneal (i.p.) Injection of 65 mg/kg streptozotocin (dissolved in citrate buffer, pH 4.5), followed by the i.p. administration of 110 mg/kg of nicotinamide (dissolved in normal saline) [16]. Hyperglycemia was confirmed by elevated blood glucose levels at 72 h and then on day 7 after injection. Those animals with fasting blood glucose level greater than 200 mg/dl were considered as diabetic and were used for diabetic neuropathy studies.

Experimental design
Diabetic rats were randomly divided into five groups each consisting of six animals.
Group I: Normal control rats (distilled water 10 ml/kg, p. o.).
Group II: Diabetic control rats.
Group III: Diabetic rats treated with 10 mg/kg coenzyme Q10 (1% aqueous solution of Tween 80, p. o.) [17].
Group IV: Diabetic rats treated with rosuvastatin (10 mg/kg, p. o) [18].
Effect of coenzyme Q10, rosuvastatin or combination on both on (A) Muscular grip strength (B) Paw withdrawal response (C) Tail flick response

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

Effect of coenzyme Q10, rosuvastatin or combination of both on markers of oxidative stress in sciatic nerve tissue

The content of MDA, end product of lipid peroxidation and marker of oxidative stress was significantly (P < 0.001) increased in sciatic nerve tissue of diabetic control rats as compared to non diabetic rats after six weeks of study. There was a significant (P < 0.001) decrease in the levels of GSH, an endogenous antioxidant and anti-oxidative enzymes (SOD) in sciatic nerve tissue as compared to normal control group.

The treatment of diabetic rats with coenzyme Q10 or rosuvastatin showed a significant increase in paw withdrawal response (P < 0.001) and tail flick response (P < 0.001) as compared to diabetic control rats. Moreover, treatment with combination of both showed a significant increase in paw withdrawal response as compared to mono-therapy (coenzyme Q10 or rosuvastatin).

Histopathological studies

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.
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) (fig 3).

**DISCUSSION**

It was previously reported that streptozotocin is most commonly used to induce diabetes in experimental animals and administration of streptozotocin-nicotinamide caused diabetic neuropathy [24,25]. Development of diabetic neuropathy was evident from alteration in muscle grip strength, nociception (paw withdrawal and tail flick response) and biochemical changes including oxidative stress. In the present study, it was shown that after six weeks of streptozotocin-nicotinamide treatment, muscular grip strength in diabetic rats was found to be reduced as compared to normal control rats. Nociception was evaluated by increased in paw withdrawal response and tail flick response (hyperalgesia). These results are in accordance with the earlier study in which it was shown that metformin alone produced a beneficial effect on diabetic nephropathy [26-28]. However, the treatment of diabetic rats with coenzyme Q10 or rosuvastatin or their combination showed a significant increase in muscular grip strength as compared to diabetic control rats. On the other hand, co-administration of coenzyme and rosuvastatin showed a significant increase in muscular grip strength than when coenzyme Q10 or rosuvastatin administered singly. Coenzyme Q10 or rosuvastatin or coenzyme Q10 + rosuvastatin treated rats showed a significant decrease in paw withdrawal response and tail flick response when compared to diabetic control rats. In this study, there was a significant increase MDA level and decrease in the level of GSH, an endogenous antioxidant and antiperoxidative enzymes (SOD) in the untreated diabetic rat sciatic nerve. Thus, it was concluded that the elevated level of MDA might be responsible for the decrease in enzymatic and non-enzymatic antioxidant of defense systems in diabetic rats. Similarly, in an earlier study, it was shown that increased MDA level and depletion of GSH and SOD have been found in sciatic nerve of diabetic rats [29-31]. In our study, it was shown that treatment with coenzyme Q10 or rosuvastatin or their combination prevented the increased in the levels of MDA and decreased GSH, SOD in sciatic nerve. Histopathological study of sciatic nerve of rats in diabetic group showed a significant degeneration of nerve tissue, while combined treatment of coenzyme Q10 and rosuvastatin showed normal sciatic nerve growth.

**CONCLUSION**

These results indicate that treatment with coenzyme Q10 or rosuvastatin showed significant neuroprotective effect against STZ-nicotinamide induced diabetic nephropathy. However, concomitant administration of both showed a better neuroprotective effect than coenzyme Q10 or rosuvastatin alone treatment by virtue of amelioration of lipid peroxidation as well as due to improvement in muscular grip strength, paw withdrawal response and tail flick response along with histopathological changes. Finally, it was concluded that adjuvant therapy of coenzyme Q10 with antidiabetic drug might prevent or delay the diabetic neuropathy.

**CONFLICTING INTEREST**

The Author(s) declare(s) that they have no conflicts of interest to disclose.

**REFERENCES**


