Antiatherogenic, hepatoprotective, and hypolipidemic effects of coenzyme Q10 in alloxan-induced type 1 diabetic rats

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Abstract

BACKGROUND: Diabetes mellitus, one of the leading metabolic syndromes, accounts for highest morbidity and mortality worldwide. In this study, we examined possible protective effect of coenzyme Q10 on lipid profile, atherogenic index, and liver enzyme markers in alloxan-induced type 1 diabetic rats.

METHODS: A total of 30 male rats were randomly divided into three groups; group 1 as control, group 2 diabetic untreated, and group 3 treatments with coenzyme Q10 by 15 mg/kg i.p. daily, respectively. Diabetes was induced in the second and third groups by alloxan injection subcutaneously. After 8 weeks, the levels of fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), very low-density lipoprotein (VLDL), high density lipoprotein (HDL), atherogenic index, atherogenic coefficient, cardiac risk ratio, and the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) of all groups were analyzed. Data were analyzed using non-parametric Mann-Whitney test (using SPSS) and P < 0.05 was considered as significant.

RESULTS: Coenzyme Q10 inhibited significantly the activities of ALT (11.17%), AST (19.35%) and ALP (36.67%) and decreased FBG (21.19%), TG (37.24%), TC (17.15%), LDL (30.44%), VLDL (37.24%), atherogenic index (44.24%), atherogenic coefficient (49.69%), and cardiac risk ratio (37.97%), HDL level was significantly (33.38%) increased when treated with coenzyme Q10.

CONCLUSION: The findings of this study suggest that coenzyme Q10 exert beneficial effects on the lipid profile, atherogenic index, and liver enzymes activity in alloxan-induced type 1 diabetic rats.

Keywords: Diabetes, Lipid Profile, Atherogenic Index, Rats, Liver Enzymes, Coenzyme Q10

Introduction

Diabetes mellitus, one of the leading metabolic syndromes, accounts for highest morbidity and mortality worldwide. Diabetes mellitus is characterized by abnormalities in carbohydrate, lipid and protein metabolism due to complete or relative insufficiency of insulin secretion from pancreatic β-cells and/or defect in insulin action. Oxidative stresses is a state of imbalance between oxidant and antioxidant systems. In recent times, much attention has been focused on the central and key role of oxidative stress in the pathogenesis of different diabetic complications. Several studies have shown that antioxidant treatment reduces diabetic complications. Due to increasing demand of patients for the use of natural products with anti-diabetic activity, the general trend now is to use the natural products for medicinal application in their natural available form. Polyphenols, well-known antioxidants, have also been showed to function as anti-diabetic by reducing blood glucose levels. Researchers are recently interested in investigation and research into extraction of natural antioxidants to replace synthetic antioxidants. Therefore, the research into the determination of the natural antioxidant source is very important to promote public health.

Coenzyme Q10 is a natural human ubiquinone, and it has fundamental role in mitochondrial energy (adenosine triphosphate) production in the respiratory chain. It plays a role in extra-mitochondrial redox activity in the cell membrane. Coenzyme Q10 is also antioxidant, scavenging free radicals and stabilizing lipids. It is also reported to have anti-inflammatory and immunomodulatory effects.

Date of submission: 6 Jul 2013, Date of acceptance: 1 May 2014
were anesthetized (nesdonal 50 mg/kg, i.p.), blood was obtained from Pasteur Institute of Tehran, with coenzyme Q10 by 15 mg/kg i.p. daily. Thirty male mature Sprague-Dawley rats (180-200 g) were allowed free access to food and water during the experiment. The third group was as follows: group 1 as control, group 2 as diabetic without treatment, and group 3 as diabetic treatment with coenzyme Q10 (C9538, Sigma Chemical Co., St. Louis, MO, USA). Twenty-two and one-half of the animals (10 per each). The studied animals (Table 1) (P < 0.05). The level of TG in the untreated diabetic rats was significantly (1.32-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (37.24%) inhibit the increase of glucose bioactivity in comparison with the untreated diabetic animals (Table 1) (P < 0.05). The level of TC in the untreated diabetic rats was significantly (1.49-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (17.15%) inhibit the increase of TC in comparison with the untreated diabetic animals (Table 1) (P < 0.05). The level of LDL in comparison with the untreated diabetic animals (Table 1) (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (30.44%) inhibit the increase of LDL in comparison with the untreated diabetic rats.

Materials and Methods

Experimental design

Animals

Thirty male mature Sprague-Dawley rats (180-200 g) were obtained from Pasteur Institute of Tehran, Iran, and were allowed to adapt themselves with the new location for 1 week. This study was approved by the Animal Ethics Committee of Lorestan University of Medical Sciences, Iran, with accordance to the national health and medical research council guidelines. The rats were randomly divided into three groups (10 per each). The studied groups were as follows: group 1 as control, group 2 as diabetic without treatment, and group 3 as diabetic treatment with coenzyme Q10 (C9538, Sigma Chemical Co., St. Louis, MO, USA).

Diabetes induction

Diabetes was induced after overnight fasting in the second and third groups by injection of alloxan monohydrate (120 mg/kg) subcutaneously. The beta-cell degradation by alloxan leads to release of more insulin. Because of acute hypoglycemia, the rats received 10% sucrose solution for 48 h instead of drinking water. Five days after induction of diabetes, blood samples were gathered from the end part of tails. Blood glucose was measured by glucometer and the rats with blood glucose level of ≥ 300 mg/dl (16.7 mmol/l) were considered as diabetic. During the first 5 days after diabetes induction, 1-3 rats per group died because of alloxan toxicity. The rats were kept at 12/12 dark-light period in 21 ± 3°C temperature. All animals were allowed free access to food and water ad libitum during the experiment. The third group was treated with coenzyme Q10 by 15 mg/kg i.p. daily.

The treatment was begun at the 1st day of diabetes induction. After 8 weeks treatment, animals were anesthetized (nesdonal 50 mg/kg, i.p.), blood samples were obtained from hearts and allowed to clot for 20 min in laboratory temperature and then centrifuged at 3000 rpm for 10 min for serum separation.

Biochemical study

The serum levels of fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), very low-density lipoprotein (VLDL), high density lipoprotein (HDL), atherogenic index and the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) of all groups were analyzed. FBG, TC, and TG concentrations and ALT, AST, and ALP activity were measured by biochemical analyzer using commercial kits (Olympus AU-600, Tokyo, Japan). HDL was analyzed by a Pars Azmoon kit from Iran. LDL and VLDL were determined by calculation using the Freidewald equation. The atherogenic index was determined by calculation using the Ikewuchi and Ikewuchi equation.

Statistical analysis

All values are expressed as mean ± standard error of mean. The data were compared between groups by Mann-Whitney U test. Statistical analyses were performed using the SPSS for Windows (version 13, SPSS Inc., Chicago, IL, USA) software. P-value of < 0.05 was considered as statistically significant.

Results

The level of glucose in the untreated diabetic rats was significantly (4.48-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (21.19%) inhibit the increase of glucose in comparison with the untreated diabetic animals (Table 1) (P < 0.05). The level of TC in the untreated diabetic rats was significantly (1.49-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (17.15%) inhibit the increase of TC in comparison with the untreated diabetic animals (Table 1) (P < 0.05). The level of TG in the untreated diabetic rats was significantly (1.32-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (37.24%) inhibit the increase of TG in comparison with the untreated diabetic animals (Table 1) (P < 0.05). The level of LDL in the untreated diabetic rats was significantly (2.72-fold) higher than that of control animals. The treatment of diabetic animal with coenzyme Q10 could significantly (30.44%) inhibit the increase of LDL in comparison with the untreated diabetic rats.
animals (Table 1) (P < 0.05). The level of VLDL in the untreated diabetic rats was significantly (1.32-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (37.24%) inhibit the increase of VLDL in comparison with the untreated diabetic animals (Table 1) (P < 0.05). The level of HDL in the untreated diabetic rats was significantly (1.23-fold) lower than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (33.38%) increase the level of HDL in comparison with the untreated diabetic animals (Table 1) (P < 0.05).

The level of atherogenic index (units) [\log (TG/HDL-C)] in the untreated diabetic rats was significantly (1.39-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (44.24%) inhibit the increase of atherogenic index in comparison with the untreated diabetic animals (Table 2) (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (2.45-fold) higher than that of control animals (Table 2) (P < 0.05). The level of cardiac risk ratio (TC/HDL-C) in the untreated diabetic rats was significantly (1.32-fold) higher than that of control animals (Table 1) (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (1.23-fold) lower than that of control animals (Figure 2) (P < 0.05). The activity of AST in the untreated diabetic rats was significantly (1.87-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (3.45-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (37.97%) inhibit the increase of cardiac risk ratio (TC/HDL-C) in comparison with the untreated diabetic animals (Table 2) (P < 0.05). The level of cardiac risk ratio (LDL/HDL-C) in the untreated diabetic rats was significantly (3.45-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (47.66%) inhibit the increase of cardiac risk ratio (LDL/HDL-C) in comparison with the untreated diabetic animals (Table 2) (P < 0.05).

The activity of ALP in the untreated diabetic rats was significantly (1.87-fold) higher than that of control animals. The treatment of diabetic animal with coenzyme Q10 could significantly (36.67%) inhibit the increase of ALP in comparison with the untreated diabetic animals (Figure 1) (P < 0.05). The activity of ALT in the untreated diabetic rats was significantly (1.30-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (11.17%) inhibit the increase of ALT in comparison with the untreated diabetic animals (Figure 2) (P < 0.05). The activity of AST in the untreated diabetic rats was significantly (1.83-fold) higher than that of control animals (P < 0.05). The treatment of diabetic animal with coenzyme Q10 could significantly (19.35%) inhibit the increase of \textit{AST} in comparison with the untreated diabetic animals (Figure 3) (P < 0.05).

**Table 1.** Effect of coenzyme Q10 on fasting blood glucose, triglyceride, total cholesterol, low density lipoprotein, very low density lipoprotein, and high density lipoprotein in diabetic rats

| Parameter                  | Control                             | Diabetic                      | Diabetic + coenzyme Q10       |
|----------------------------|-------------------------------------|-------------------------------|-------------------------------|
| FBG (mg/dl)                | 79.09 ± 27.66                      | 354.02 ± 58.32                | 279.07 ± 45.00 *             |
| TG (mg/dl)                 | 110.00 ± 29.66 *                   | 145.00 ± 28.01                | 91.00 ± 27.78                |
| TC (mg/dl)                 | 75.32 ± 13.33                      | 112.05 ± 26.31                | 92.83 ± 21.14 *              |
| HDL (mg/dl)               | 32.52 ± 7.75 *                     | 26.42 ± 12.49                 | 35.24 ± 7.32 *              |
| LDL (mg/dl)               | 20.80 ± 3.87 *                     | 56.63 ± 6.94                  | 39.39 ± 9.94 *              |
| VLDL (mg/dl)              | 22.00 ± 4.89 *                     | 29.00 ± 4.78                  | 18.20 ± 3.72 *              |

Values are represented as mean ± SEM coenzyme Q10. * Significant change in comparison with diabetic without treatment at P < 0.05; * Significant change in comparison with control at P < 0.05; SEM: Standard error of mean; FBG: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein

**Table 2.** Effect of coenzyme Q10 on atherogenic index, atherogenic coefficient, and cardiac risk ratio in diabetic rats

| Parameter                              | Control          | Diabetic                  | Diabetic + coenzyme Q10       |
|----------------------------------------|------------------|---------------------------|-------------------------------|
| Atherogenic index [(units) \log (TG/HDL-C)] | 0.53 ± 0.06 *    | 0.74 ± 0.06               | 0.41 ± 0.02 *                |
| Atherogenic coefficient [(TC/HDL-C)/HDL-C] | 1.32 ± 0.72      | 3.24 ± 0.87               | 1.63 ± 0.21                  |
| Cardiac risk ratio (TC/HDL-C)          | 2.32 ± 0.54 *    | 4.24 ± 0.75               | 2.63 ± 0.62 *                |
| Cardiac risk ratio (LDL/HDL-C)         | 0.62 ± 0.08 *    | 2.14 ± 0.67               | 1.12 ± 0.27 *                |

Values are represented as mean ± SEM coenzyme Q10. * Significant change in comparison with diabetic without treatment at P < 0.05; * Significant change in comparison with control at P < 0.05; SEM: Standard error of mean; FBG: Fasting blood glucose; TG: Triglyceride; HDL: High density lipoprotein cholesterol; TC: Total cholesterol; LDL: Low density lipoprotein cholesterol
Discussion

Effect of coenzyme Q10 on serum lipid profile and atherogenic index

Diabetes significantly increased serum FBG, TG, TC, VLDL, and LDL concentrations in comparison with the control group. Treatment of diabetic animals with coenzyme Q10 significantly inhibited increase of serum FBG, TG, TC, VLDL, and LDL concentrations, atherogenic index, atherogenic coefficient, and cardiac risk ratio in comparison with the untreated diabetic animals. Furthermore, treatment of diabetic animals with coenzyme Q10 significantly inhibited decrease of serum HDL concentrations in comparison with the untreated diabetic animals. There are reports that natural antioxidant such as lycopene and natural phenolic compounds have hypolipidemic effects.25,26 Furthermore, there are reports that coenzyme Q10 have hypolipidemic effects. Cicero et al. showed coenzyme Q10 could reduce serum lipoprotein (a) level in patients with high serum triglyceride levels.27 Moreover, Gao et al. showed coenzyme Q10 could reduce serum lipoprotein (a) level in patients with coronary artery diseases.28 Also, Shojaei et al. showed coenzyme Q10 could reduce serum levels of lipoprotein (a) and lipids in Maintenance Hemodialysis Patients on Statin Therapy.29 Results of our study are in accordance with others researchers’ study that showed coenzyme Q10 could reduce serum lipid and lipoprotein level. Therefore, natural antioxidant with hypolipidemic effects could prevent or be helpful in reducing the complications of lipid profile seen in diabetes patients. The mechanisms by which coenzyme Q10 can decrease high serum lipid level is not well known. The mechanism of hypolipidemic and antiatherogenic action of natural antioxidant may be due to the inhibition of dietary lipid absorption in the intestine or its production by liver or stimulation of the biliary secretion of cholesterol and cholesterol excretion in the face.30,31 Moreover, coenzyme Q10 is a lipid-soluble molecule, and it is present in sufficient amounts in lipoprotein (a). Supplementation with coenzyme Q10 can inhibit expression of lipoprotein (a) receptor and result in decreased serum lipoprotein (a).32 Also, the mechanism of hypolipidemic and antiatherogenic action of natural antioxidant may be due to the inhibition of glycation lipoproteins, enzymes and proteins that involve lipid and lipoprotein metabolism.33
Effect of coenzyme Q10 on serum ALP, ALT, and AST activity

Serum ALP, ALT, and AST activity as markers of liver function significantly were increased in the untreated diabetic animals in comparison with the control group. Treatment of the diabetic animals with coenzyme Q10 could significantly inhibit increase of serum ALP, ALT, and AST activity in comparison with the untreated diabetic animals. Treatment by coenzyme Q10 could maintain serum ALP, ALT, and AST activity of the treated animal at the same level as that of the control group. ALP, ALT, and AST are considered to be biochemical markers for assessing liver function. Hepatotoxicity is evidenced by an elevation of the serum marker enzymes.34,35

There are reports that natural antioxidant such as leptin and melatonin reduced these liver enzymes markers.36,37 Also, there are reports that coenzyme Q10 have hepatoprotective effects.38 Mabuchi et al. showed coenzyme Q10 could reduce serum ALT and AST activities.38 Moreover, Ali et al. showed coenzyme Q10 could reduce serum ALT and AST activities on CCl4-induced liver injury in rats.39 Also, Amimoto et al. that is chemically damaged livers pretreated with coenzyme Q10 showed a decrease in the activity of serum ALT and AST.40 Results of our study are in accordance with others researchers’ study that showed coenzyme Q10 could reduce serum ALT, AST, and ALP activities. Therefore, natural antioxidant with hepatoprotective action could prevent or be helpful in reducing the complications of hepatic damage seen in diabetes patients.41

Researchers indicated that coenzyme Q10 is found to possess a good antioxidant activity.35 Also researchers reported the role of oxidative stress as a central factor in onset and progression of diabetic complications such as hyperlipemia and hepatic damage.4,42 Therefore, numerous reports and our results that showed efficacy of antioxidative supplements administration in the prevention of diabetic complications. Since antioxidant therapy is as one of the most important treatment strategies for diabetic patients for the prevention and slowing of diabetic complications progression such as hyperlipemia and hepatic damage.

This study has limitation in which we assumed the groups 2 diabetic without treatment with placebo.

Conclusion

This study showed that coenzyme Q10 has beneficial effects, in reducing the elevated serum lipid profile, atherogenic index and liver enzyme markers of alloxan-induced-diabetic rats. Hence, attenuation of lipid profile, atherogenic index and liver enzyme markers can decrease the risk of cardiovascular death and hepatic damage in diabetic patients.

Acknowledgments

The authors wish to thank Deputy of Research and Razi Herbal Research Center of Lorestan Medical University, Lorestan, Iran.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Ahmadvand H, Ghasemi-Dehnoo M. Antiatherogenic, hepatoprotective, and hypolipidemic effects of coenzyme Q10 in alloxan-induced type 1 diabetic rats. ARYA Atheroscler 2014; 10(4): 192-8.