ORIGINAL ARTICLE

Effects of Coenzyme Q_{10} on Hemoglobin A_{1C}, Serum Urea and Creatinine in Alloxan-Induced Type 1 Diabetic Rats

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ABSTRACT

Coenzyme Q_{10} is a natural antioxidant and free radicals scavenger. In the present study, we examined effect of coenzyme Q_{10} on hemoglobin A_{1C}, serum urea and creatinine in alloxan-induced Type 1 diabetic rats. Thirty Sprage-Dawley male rats were divided into three groups randomly; group one as control, group two diabetic untreatment, and group three treatments with coenzyme Q_{10} (15 mg/kg i.p daily), respectively. Diabetes was induced in the second and third groups by alloxan injection subcutaneously. After 8 weeks, animals were anaesthetized; blood samples were collected to measure the hemoglobin A_{1C}, serum glucose, urea and creatinine. Coenzyme Q_{10} significantly decreased hemoglobin A_{1C}, serum glucose, urea and creatinine. Coenzyme Q_{10} exerts beneficial effects on the hemoglobin A_{1C} and serum glucose in alloxan-induced type 1 diabetic rats.

Keywords: *Diabetes, Hemoglobin A_{1C}, Serum, Glucose, Rat, Coenzyme Q_{10}*

Hyperglycemia is confounded for the complications of diabetes because hyperglycemia directly causes glycation of proteins, lipids and nucleic acid that injures cells and induces lipid peroxidation [1]. Also, antioxidant and antioxidative enzyme activities are reduced due to glycation or increased lipid peroxidation products [2]. A number of natural antioxidant such as vitamin E and phenolic compounds are known to have hypoglycemic, hypolipidemic or both activities [3]. Chemical drugs have many side effects; therefore, screening for new antidiabetic sources from natural antioxidants is still attractive because they are mostly safe and are good alternative for treatment of diabetes mellitus. A growing body of research indicates that nutritional deficiencies such as antioxidants contribute to the development of diabetes.

Coenzyme Q_{10} is a natural human ubiquinone, and it has fundamental role in mitochondrial energy (ATP) production in the respiratory chain [4,5]. Coenzyme Q_{10} is also antioxidant, scavenging free radicals and inhibiting lipid peroxidation [6-8]. The antioxidant effect of coenzyme Q_{10} is greater than vitamin E [8]. Coenzyme Q_{10} is also known to enhance the availability of other antioxidants such as vitamin C, vitamin E and beta-caroten [9]. Since the protective effects of coenzyme Q_{10} on hyperglycemia and hemoglobin A_{1C} status in alloxan-induced type 1 diabetic rats have not previously been reported; the objectives of the present study were to investigate amelioration of altered glucose, hemoglobin A_{1C}, serum urea and creatinine by coenzyme Q_{10} in alloxan-induced type 1 diabetic rats.

MATERIALS AND METHODS

Experimental designee

Animals

Thirty male mature Sprague–Dawley rats (180-200 g) were obtained from Pasteur Institute of Tehran and were allowed to adapt themselves with the new location for one week. This study was approved by the Animal

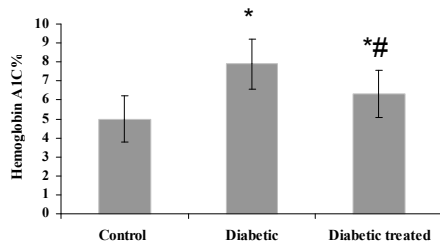Ethics Committee of the Medical University of Lorestan

Fig 1. The effect of coenzyme Q_{10} on hemoglobin A_{1C} in alloxan-induced diabetic rats.
*$p < 0.05$ as compared with control group.
#$p < 0.05$ as compared with diabetic without treatment group.

Fig 2. The effect of coenzyme Q_{10} on serum glucose in alloxan-induced diabetic rats.
*$p < 0.05$ as compared with control group.
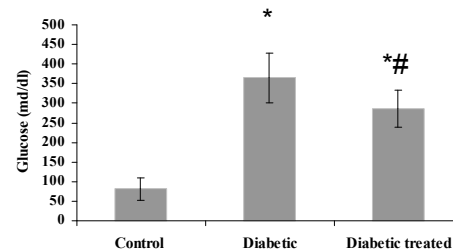#$p < 0.05$ as compared with diabetic without treatment group.

with accordance to the National Health and Medical Research Council guidelines. The rats were divided to three groups (10 per each). The studied groups were as follows: group 1 as control, group 2 as diabetic without treatment and 3rd group as diabetic treatment with coenzyme Q_{10}.

Diabetes induction

Diabetes was induced after overnight fasting in the second and third groups by injection of alloxan monohydrate (120 mg/kg) subcutaneously [10]. 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 ≥300 mg/dl (16.7 mmol/L) were considered as diabetic [11-13]. During the first five 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 Q_{10} by 15 mg/kg i.p daily [12]. The treatment was begun at the first 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 minutes in laboratory temperature and then centrifuged at 3000 rpm for 10 minutes for serum separation [13]. Also, blood sample were used to measure the hemoglobin A1C.

Level of hemoglobin A1C, serum glucose, urea and creatinine

The hemoglobin A_{1C} was determined using a hemoglobin A_{1C} assay kit (Randox Lab., Ltd., UK) according to the manufacturer's protocol. Also glucose, urea and creatinine in the serum were determined by biochemical analyzer using commercial kits (Olympus AU-600, Tokyo, Japan).

Statistical analysis

All values were expressed as mean ± SEM. The data were compared between groups by Mann-Whitney U test. Statistical analyses were performed using the SPSS 13 for windows software. A *p* value of < 0.05 was considered statistically significant.

RESULTS

The level of hemoglobin A_{1C} in the untreated diabetic rats was significantly (1.58-fold) higher than that of control animals. The treatment of diabetic animal with coenzyme Q_{10} could significantly (20%) inhibit the increase of hemoglobin A_{1C} in comparison with the untreated diabetic animals (Fig 1). The level of glucose in the untreated diabetic rats was significantly (4.5-fold) higher than that of control animals. The treatment of diabetic animal with coenzyme Q_{10} could significantly (21%) inhibit the increase of glucose in comparison with the untreated diabetic animals (Fig 2). The level of urea in the untreated diabetic rats was significantly (1.5-fold) higher than that of control animals. The treatment of diabetic animal with coenzyme Q_{10} could significantly (29.5%) inhibit the increase of urea in comparison with the untreated diabetic animals (Fig 3). The level of creatinine in the untreated diabetic rats was significantly (1.3-fold) higher than that of control animals. The treatment of diabetic animal with coenzyme Q_{10} could significantly (14.5%) inhibit the increase *of* creatinine in comparison with the untreated diabetic animals (Fig 4).

DISCUSSION

Diabetes significantly increased serum urea and creatinine in comparison with the control group. Elevations of serum urea and creatinine were confirmed with development of diabetic nephropaty in the untreated diabetic rats [14]. Treatment of diabetic animals with coenzyme Q_{10} significantly inhibited increase of serum urea and creatinine and progression of
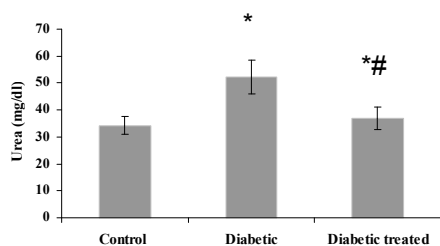
Fig 3. The effect of coenzyme Q_{10} on serum urea in alloxan-induced diabetic rats.
*$p < 0.05$ as compared with control group.
#$p < 0.05$ as compared with diabetic without treatment group.

Fig 4. The effect of coenzyme Q_{10} on serum creatinine in alloxan-induced diabetic rats.
*$p < 0.05$ as compared with control group.
#$p < 0.05$ as compared with diabetic without treatment group.

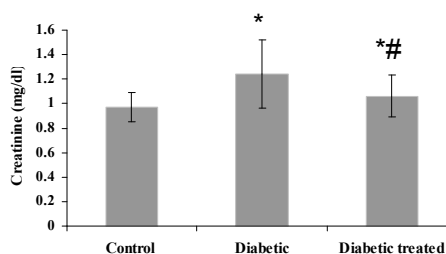diabetic nephropathy.in comparison with the untreated diabetic animals. This study showed that coenzyme Q_{10} has beneficial effects, in reduction the increased hemoglobin A_{1C} had protective effects on hyperglysemia in alloxan-induced diabetic rats. There are much evidence that oxidative stress play a key role in the most pathogenic pathway of diabetic injuries. Free radicals such as superoxide can induce cell and tissue injuries throughout lipid peroxidation and increase carcinogenesis, inflammation, early aging, cardiovascular diseases and tissue damage in diabetes [15,16]. Antioxidants such as vitamin E, coenzyme Q_{10} and antioxidant enzymes protect the cells against oxidative-stress-mediated cellular injuries by converting the toxic free radicals to non-toxic products [17,18]. There are reports that natural antioxidant such as vitamin E [19], caffeic acid [20,21], lipoic acid, quercetin [22], melatonin [23] and natural phenolic compounds have protective effects on hyperglcemia in diabetics disease [24,25]. Also, these compounds could reduce hemoglobin A_{1C} level in diabetic patients [17-25]. There are reports that coenzyme Q_{10} have protective effects on lipid peroxidation and in vitro or in vivo LDL oxidation. The inhibitory effect of coenzyme Q_{10} on LDL oxidation is better than vitamin E [26]. Researchers showed coenzyme Q_{10} could reduce serum lipid peroxidation level in diabetic patients [26]. Moreover, researchers showed coenzyme Q_{10} could reduce serum lipid peroxidation level in patients with coronary artery diseases [27].

Results of our study are in accordance with other researchers' study that showed coenzyme Q_{10} similar to others antioxidants such as vitamin E and lipoic acid could reduce hemoglobin A_{1C} and prevent hyperglycemia. Therefore, natural antioxidant with protective effects on hyperglycemia could prevent or be helpful in reducing the complications that related to hyperglycemia in diabetes patients. Although the detailed molecular protective mechanisms of coenzyme Q_{10} can not be fully explained by our results, our results are satisfactory. Coenzyme Q_{10} as lipid soluble antioxidant with multi beneficial properties can be introduced to diabetic patients without diabetic nephropathy for inhibition of progression of diabetic

nephropathy. This study showed that coenzyme Q10 has beneficial effects in decreasing the elevated hemoglobin A_{1C}, urea and creatinine and protective effects on hyperglycemia in alloxan-induced diabetic rats. Hence, attenuation of hyperglycemia, hemoglobin A_{1C}, urea and creatinine can decrease diabetic complication such as nephropathy in diabetic patients.

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REFERENCES

1. Lin Y, Sun Z. Current views on type 2 diabetes. *J Endocrinol* 2010; 204:1-11.

2. Maritim AC, Sanders RA, Watkins JB. Diabetes, Oxidative Stress, and Antioxidants: A Review. *J Biochem Mol Toxicol* 2003; 17:24-38.

3. Drissi A, Girona J, Cherki M, Godàs G, Derouiche A, El Messal M, Saile R, Kettani A, Solà R, Masana L, Adlouni A. Evidence of hypolipemiant and antioxidant properties of argan oil derived from the argan tree (Argania spinosa). *Clin Nutr* 2004; 23:1159-66.

4. Littarru GP, Tiano L. Bioenergetic and antioxidant properties of coenzyme Q10: recent developments. *Mol Biotechnol* 2007; 37:31-7.

5. Somayajulu M, McCarthy S, Hung M, Sikorska M, Borowy-Borowski H, Pandey S. Role of mitochondria in neuronal cell death induced by oxidative stress; neuroprotection by Coenzyme Q10. *Neurobiol Dis* 2005; 18:618-27.

6. Bélanger MC, Mirault ME, Dewailly E, Berthiaume L, Julien P. Environmental contaminants and redox status of coenzyme Q10 and vitamin E in Inuit from Nunavik. *Metabolism* 2008; 57:927-33.

7. Mabuchi H, Higashikata T, Kawashiri M, Katsuda S, Mizuno M, Nohara A, Inazu A, Koizumi J, Kobayashi J. Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. *J Atheroscler Thromb* 2005; 12:111-9.

8. Niklowitz P, Menke T, Andler W, Okun JG. Simultaneous analysis of coenzyme Q10 in plasma, erythrocytes and platelets: comparison of the antioxidant level in blood cells and their

environment in healthy children and after oral supplementation in adults. *Clin Chim Acta* 2004; 342:219-26.

9. Shekelle P, Morton S, Hardy ML. Effect of supplemental antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease. *Evid Rep Technol Assess* 2003; 83:1-3.

10. Fernandes NP, Lagishetty CV, Panda VS, Naik SR. An experimental evaluation of the antidiabetic and antilipidemic properties of a standardized Momordica charantia fruit extract. *BMC Complement Altern Med* 2007; 24:29-37.

11. Haidara MA, Mikhailidis DP, Rateb MA, Ahmed ZA, Yassin HZ, Ibrahim IM, Rashed LA. Evaluation of the effect of oxidative stress and vitamin E supplementation on renal function in rat with streptozotocin-induced type 1 diabetes. *J Diabet Complications* 2009; 23:130–6.

12. Kim YH, Moon YI, Kang YH, Kang JS. Effect of Coenzyme Q10 and green tea on plasma and liver lipids, platelet aggregation, TBARS production and erythrocyte Na leak in simvastatin treated hypercholesterolmic rats. *Nutr Re. Pract* 2007; 1:298-304.

13. Tavafi M, Ahmadvand H, Tamjidipoor A, Delfan B, Khalatbari AR. Satureja khozestanica essential oil ameliorates progression of diabetic nephropathy in uninephrectomized diabetic rats. *Tissue Cell* 2011; 43:45-51.

14. Morsy MD, Hassan WN, Zalat SI. Improvement of renal oxidative stress markers after ozone administration in diabetic nephropathy in rats. *Diabetol Metabolic Syndrome* 2010, 2:29.

15. Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, Zoccali C. Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. *Nephrol Dial Transplant* 2003; 18:1272-80.

16. Jen-Kun L, Shu-Huei T. Chemoprevention of Cancer and Cardiovascular Disease by Resveratrol. *Proc Natl Sci Counc ROC (B)* 1999; 23:99-106.

17. McMahon M, Skaggs BJ, Sahakian L, Grossman J, FitzGerald J, Ragavendra N, Charles-Schoeman C, Chernishof M, Gorn A, Witztum JL, Wong WK, Weisman M, Wallace DJ, La Cava A, Hahn BH. High plasma leptin levels confer increased risk of atherosclerosis in women with systemic lupus erythematosus, and are associated with inflammatory oxidised lipids. *Ann Rheum Dis* 2011; 70:1619-24.

18. Cornejo-Garcia JA, Mayorga C, Torres MJ, Fernandez TD, R-Pena R, Bravo I, Mates JM, Blanca M. Anti-oxidant enzyme activities and expression and oxidative damage in patients with non-immediate reactions to drugs. *Clin Exp Immunol* 2006; 145:287-95.

19. Roldi LP, Pereira RV, Tronchini EA, Rizo GV, Scoaris CR, Zanoni JN, Natali MR. Vitamin E (alpha-tocopherol) supplementation in diabetic rats: effects on the proximal colon. *BMC Gastroenterol* 2009; 23:88.

20. Jung UJ, Lee MK, Park YB, Jeon SM, Choi MS. Antihyperglycemic and antioxidant properties of caffeic acid in db/db mice. *J Pharmacol Exp Ther* 2006; 31:476-83.

21. Kaneto H, Kajimoto Y, Miyagawa J, Matsuoka T, Fujitani Y, Umayahara Y, Hanafusa T, Matsuzawa Y, Yamasaki Y, Hori M. Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity. *Diabetes* 1999; 48:2398-406.

22. Balkis Budin S, Othman F, Louis SR, Abu Bakar M, Radzi M, Osman K, Das S, Mohamed J. Effect of alpha lipoic acid on oxidative stress and vascular wall of diabetic rats. *Rom J Morphol Embryol* 2009; 50:23-30.

23. Garfinke D, Zorin M, Wainstein J, Matas Z, Laudon M, Zisapel N. Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study Diabetes, Metabolic Syndrome and Obesity: Targets Therapy 2011; 4:307–13.

24. Bose KS, Agrawal BK. Effect of lycopene from tomatoes (cooked) on plasma antioxidant enzymes, lipid peroxidation rate and lipid profile in grade-I hypertension. *Ann Nutr Metab* 2007; 51:477-81.

25. Kaliora AC, Dedoussis GV. Natural antioxidant compounds in risk factors for CVD. *Pharmacol Res* 2007; 56:99-109.

26. Sena CM, Nunes E, Gomes A, Santos MS, Proença T, Martins MI, Seiça RM. Supplementation of coenzyme Q10 and alpha-tocopherol lowers glycated hemoglobin level and lipid peroxidation in pancreas of diabetic rats. *Nutr Res* 2008; 28:113-21.

27. Thomas SR, Witting PK, Stocker R. A role for reduced coenzyme Q in atherosclerosis? Biofactors 1999; 9:207-24.

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