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The Effects of Coenzyme Q₁₀ on Inflammation Markers in Streptozotocin-Induced Diabetic Rats

Deniz Uluisik & Ercan Keskin

ABSTRACT

Background: Coenzyme Q₁₀ is a well-known cofactor in the mitochondrial electron transport chain required for ATP production. Coenzyme Q₁₀ is recognized as an intracellular antioxidant that protects cell membrane phospholipids, mitochondrial membrane protein, and plasma low-density lipoprotein against oxidative damage caused by free radicals. Diabetes and its complications have been related to increased levels of free radicals and systemic proinflammatory cytokines and to an abnormal lipid profile. The aim of this study was to investigate the effects of coenzyme Q₁₀ supplementation on some cytokine levels in streptozotocin-induced diabetic rats.

Materials, Methods & Results: In this study, 38 healthy, adult male rats were used. The rats were divided into 5 groups. All animals were housed in separated cages during the four weeks. The animals in group 1 was fed standard rat pellets for 4 weeks. It was administered at 0.3 mL corn oil intraperitoneally daily for four weeks in group 2 animals. The animals in group 3 was injected intraperitoneally with 10 mg/kg CoQ₁₀ daily for 4 weeks. Group 4 was made diabetic by subcutaneous injections of streptozotocin at dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) single daily dose for two days and group 5 was made diabetic by subcutaneous injections of streptozotocin at dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) single daily dose for two days and then was injected intraperitoneally with 10 mg/kg CoQ₁₀ daily for 4 weeks. During the experiment, three animals from group 4 and one animals from group 5 were died due to streptozotocin-induced hypoglycemia. At the end of the study, blood samples were taken from all animals. In these blood samples, IL-4, IL-6, IL-10 and TNF- α plasma levels were determined with ELISA using sandwich enzyme-linked immunosorbent method via commercial kits. In this study, IL-4 level as an anti-inflammatory cytokine significantly decreased ($P < 0.05$) with diabetes induction compared to control group level. IL-10 level in diabetic group was statistically different ($P < 0.05$) from control group level. CoQ₁₀ application to diabetic animals improved the falling in IL-10 level of diabetic group ($P < 0.05$). IL-6 and TNF- α levels in diabetic group significantly increased ($P < 0.05$) in parallel with each other compared to control group levels. The same parameters were reduced ($P < 0.05$) by CoQ₁₀ application in diabetic animals.

Discussion: In this study, the occurred changes in pro- and anti-inflammatory cytokines with experimentally induced diabetes are expected results and these results are consistent with some studies related diabetes. These results may be considered to hazardous effects and inflammation caused by diabetes on liver, pancreas and other tissues. CoQ₁₀ suppressed the increments in plasma pro-inflammatory cytokine levels, whereas it restored the reducing in anti-inflammatory cytokine levels arising due to diabetes. The obtained results from this study after CoQ₁₀ application supported similar studies used CoQ₁₀ application against deleterious effects of diabetes in animals and humans. Therefore, it is possible to say that CoQ₁₀ may play important role in regulation of imbalance between inflammation markers in diabetes conditions and further studies are needed to clear the beneficial effects of CoQ₁₀ treatment on the other inflammation markers in diabetes status.

Keywords: CoQ₁₀, cytokine, diabetes, rats.

INTRODUCTION

Type 1 diabetes is an autoimmune disease and characterized with islet β -cells destroying by a response mediated by T lymphocytes that react specifically to one or more β -cell proteins [3]. Type 1 diabetes also is accepted as a Th1-mediated disease and CD4- and CD8-positive T lymphocytes secreting IFN- γ are responsible for β -cell destruction, thus favoring cellular immunity [22]. However, Th1 activities are downregulated by Th2 cells secreting IL-4 and IL-10. In type 1 diabetes conducted animal models, it was reported that increments in Th2 activities prevented autoimmune responses augmented by Th1 cells in diabetes [14,20,23,29]. Rabinovitch [21] reported that cytokines as regulators and mediators of immune responses might have important roles in the pathogenesis of IDDM.

Coenzyme Q₁₀ (CoQ₁₀) is required for ATP production in the mitochondrial electron transport chain as a well-known cofactor. CoQ₁₀ which is known ubiquinone or ubidecarenone is synthesized endogenously in organisms and can also be received from exogenous food sources [27]. In addition to its important role in cell energy metabolism, the ubiquinol form of CoQ₁₀ has potent lipophilic antioxidant effects. This function was accomplished either directly via protecting cellular components from free radicals or indirectly through regeneration of other endogenous antioxidants [4,5]. In experimental studies, it has been demonstrated antioxidant, anti-inflammatory and ATP-regenerative properties of CoQ₁₀ in various diseases such as gastric ulcer, osteoarthritis and diabetes [6,7,15,16].

The study was conducted to determine the effects of coenzyme Q₁₀ on inflammation markers in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

In this study, 38 healthy, adult male Wistar Albino rats were used. The animals were housed in separated cages during the four weeks experiment and allowed free access to water and standard pellets. Diabetes was induced by subcutaneous injection of streptozotocin at a dose of 40 mg/kg daily in 0.1 M citrate buffer (pH 4.5) single daily dose for 2 days. To prevent the streptozotocin-induced hypoglycemia, rats received 5% dextrose solution after 6 h of streptozotocin administration for next 3 days. After 1 week, induction of diabetes was verified by measuring blood glucose level with strips using glucometer

(PlusMED Accuro)² via the tail vein. Animals having a blood glucose level higher than 250 mg/dL were considered diabetic and included in the experiments. The mean weights of all groups were similar. The rats were divided into 5 groups. The animals in group 1 (n = 6) were fed standard rat pellets for 4 weeks. It was administered at 0.3 mL corn oil intraperitoneally daily for 4 weeks in group 2 (n = 6) animals. The animals in group 3 (n = 6) was injected intraperitoneally with 10 mg/kg CoQ₁₀ (Coenzyme Q₁₀)¹ daily for 4 weeks. Group 4 (n = 7) was made diabetic by subcutaneous injections of streptozotocin at dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) single daily dose for two days and group 5 (n = 9) was made diabetic by subcutaneous injections of streptozotocin in the same way and then was injected intraperitoneally with 10 mg/kg CoQ₁₀ daily for 4 weeks. During the experiment, three animals from group 4 and one animals from group 5 were died due to streptozotocin-induced hypoglycemia.

At the end of the study, blood samples were taken from all animals. In these blood samples, IL-4, IL-6, IL-10 and TNF- α plasma levels were determined with ELISA (Biotek ELx800)³ using sandwich enzyme-linked immunosorbent method via commercial kits (Cytokine kits)⁴.

The data were analyzed using one-way ANOVA (SPSS 17). Differences among the groups were determined by Duncan's multiple range test. Differences were considered significant at $P < 0.05$.

RESULTS

In this study, IL-4 level as an anti-inflammatory cytokine significantly decreased ($P < 0.05$; Table 1) with diabetes induction compared to control group level. Although IL-4 level in diabetic group treated with CoQ₁₀ was found to be higher than diabetic group, this change was not important. IL-10 level in diabetic group was statistically different ($P < 0.05$; Table 1) from control group level. CoQ₁₀ application to diabetic animals improved the falling in IL-10 level of diabetic group ($P < 0.05$; Table 1). IL-6 and TNF- α levels in diabetic group significantly increased ($P < 0.05$; Table 1) in parallel with each other compared to control group level. The same parameters were reduced ($P < 0.05$; Table 1) by CoQ₁₀ application in diabetic animals. There are no differences among control, oil and CoQ₁₀ groups regarding to IL-4, IL-6, IL-10 and TNF- α levels.

Table 1. Effect of Coenzyme Q₁₀ on plasma IL-4, IL-6, IL-10 and TNF- α levels in streptozotocin-induced diabetic rats (Mean \pm SE).

Group	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	TNF- α (pg/mL)
Group 1	8.98 \pm 1.19 ^a	55.73 \pm 4.81 ^c	51.58 \pm 3.65 ^a	96.28 \pm 4.03 ^c
Group 2	8.52 \pm 0.96 ^a	53.52 \pm 5.63 ^c	50.53 \pm 3.32 ^a	93.67 \pm 4.21 ^c
Group 3	9.13 \pm 0.63 ^a	50.78 \pm 4.31 ^c	53.35 \pm 5.22 ^a	98.57 \pm 5.76 ^c
Group 4	5.89 \pm 0.57 ^b	81.87 \pm 2.48 ^a	28.36 \pm 3.65 ^c	143.59 \pm 7.63 ^a
Group 5	7.52 \pm 0.80 ^{ab}	68.93 \pm 2.27 ^b	39.61 \pm 2.58 ^b	123.43 \pm 4.48 ^b

The difference between mean values with different superscripts in the same column is significant at the $P < 0.05$ level. Group 1. control; group 2. oil; group 3. CoQ₁₀; group 4. diabetes; group 5. CoQ₁₀ and diabetes.

DISCUSSION

Hyperglycemia and hyperlipidemia in diabetes are associated with diminished antioxidant enzymes production and increased formation of reactive oxygen species (ROS) [19]. Excessive ROS provokes inflammation and developed pancreatitis triggers systemic inflammatory response via release of mediators from immune cells [1,18,25]. In consistence with above acknowledgement, we have found the increase in pro-inflammatory cytokines with diabetes compared to control group in our study ($P < 0.05$; Table 1). In our study, the important increases in IL-6 and TNF- α levels with diabetes supported the data noted by Rabinovitch [21].

Several studies reported that anti-inflammatory cytokines (IL-4 and IL-10) have been founded to be decreased or unchanged [2,11,14,21]. In the experiment, IL-4 and IL-10 levels significantly decreased ($P < 0.05$; Table 1) in diabetic rats when compared to control group. This result supported the previous reports about the same cytokines obtained from diabetic rats. In diabetic rats IL-10 level showed the significant decrease [2]. Saxena *et al.* [26] have considered diabetes as a metabolic pro-inflammatory disorder that affected highly levels of circulating cytokines via severe hyperglycemia.

In the present study, CoQ₁₀ injection for four weeks to the diabetic animals resulted significantly decreases ($P < 0.05$; Table 1) IL-6 and TNF- α levels compared to diabetic group animals. Our findings are agreement with many studies. CoQ₁₀ significantly attenuated TNF- α level in ulcerative colitis in rats [7]. On the other hand, IL-6 and TNF- α levels were decreased by CoQ₁₀ application in patients with multiple sclerosis [24]. It has been reported that TNF- α level reverted with administration of CoQ₁₀ in rats with acute

pancreatitis [18]. These effects of CoQ₁₀ on cytokines can be attributed to its anti-inflammatory properties. The anti-inflammatory mechanisms of CoQ₁₀ are exactly unknown [24]. However, CoQ₁₀ have free radical scavenging activity and ability to inhibit the activation of NF-KB signaling pathway [8]. In addition, it has been reported that CoQ₁₀ have antiinflammatory effects through decrease the release of pro-inflammatory cytokines and COX-2 expression during inflammatory injury [13].

CoQ₁₀ application to diabetic animals improved the falling in IL-10 level of diabetic group ($P < 0.05$; Table 1) in this study. It has been suggested that high concentration of glucose causes high production of intracellular ROS consequently resulting low production anti-inflammatory cytokines and high production pro-inflammatory cytokines [2,9,17,28]. Thus, the increase IL-10 level with CoQ₁₀ treatment in diabetic group may be considered the antioxidative effects of CoQ₁₀. Literature reported that CoQ₁₀ treatment provoked the expression of IL-10 in experimental periodontitis rats [10] and that CoQ₁₀ administration boosted the IL-10 level in rats with acute pancreatitis [18]. Our results are in agreement with these studies.

Although the reducing in IL-4 level was alleviated by CoQ₁₀ application to diabetic animals compared with the diabetic group levels, this change was not important. It has been determined that CoQ₁₀ supplementation didn't alter IL-4 levels in patient with multiple sclerosis [24]. On the other hand, administration of CoQ₁₀ in neuropathic pain rats led to the decrease in IL-4 level [12].

In summary, CoQ₁₀ application for four weeks in streptozotocin-induced diabetic rats resulted in decreasing levels of pro-inflammatory cytokines and

improved levels of anti-inflammatory cytokines. It may be due to its antioxidant and anti-inflammatory properties, but further studies are needed to elucidate the effects of CoQ₁₀ application on inflammation and regulation of cytokines.

MANUFACTURERS

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Ethical approval. All experimental procedures were approved (number 2015/50) by the Ethical Committee of Selcuk University Experimental Medicine Research and Application Center, Konya, Turkey.

Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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