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RESEARCH ARTICLE

Effects of Coenzyme Q_{10} on Lipid Profile in Streptozotocin Induced Diabetic Rats

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Streptozotosin ile Diyabet Oluşturulan Ratlarda Koenzim Q10'un Lipit Profil Üzerine Etkileri

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Öz

Amaç: Çalışma deneysel diyabet oluşturulan ratlarda Koenzim Q_{10}'un lipit profili üzerine etkilerini değerlendirmek amacıyla yapıldı.

Gereç ve Yöntem:. Çalışmada 38 yetişkin erkek Wistar Albino rat beş gruba ayrıldı. Grup I'deki hayvanlara herhangi bir uygulama yapılmadı. Grup II'deki hayvanlara günde 0.3 ml mısır yağı dört hafta boyunca intraperitoneal olarak uygulanmıştır. Grup III'deki hayvanlara günde 0.3 ml mısır yağında çözdürülen 10 mg/kg CoQ10 dört hafta boyunca intraperitoneal olarak uygulandı. Grup IV'deki hayvanlarda, günde tek doz olarak iki gün boyunca 40 mg/kg subkutan streptozotosin enjeksiyonu ile diyabet oluşturuldu. Grup V'deki hayvanlarda, grup IV'de uygulanan protokolle diyabet oluşturuldu ve daha sonra bu hayvanlara dört hafta boyunca 0.3 ml mısır yağında çözdürülen 10 mg/kg CoQ10 intraperitoneal olarak uygulandı. Tüm gruplarda plazma total kolesterol, trigliserit, HDL, LDL, insülin ve glikoz düzeyleri belirlendi. Karaciğer kesitlerinde lipid damlacıkları içeren hücrelerin boyanma yoğunluğu değerlendirildi.

Bulgular: Deneysel diyabet, kolesterol, trigliserit ve LDL seviyelerini artırırken, bu parametreler diyabetik gruba göre diyabetik ratlara CoQ10 uygulaması ile azalmıştır (P<0.05). Plazma HDL düzeyi diyabetik grupta kontrol grubundan daha düşüktü ve diyabetik ratlara CoQ10 uygulamasıyla plazma HDL düzeyi diyabetik gruba kıyasla anlamlı olarak yükseldi (P<0.05). Diyabet grubunda lipid damlacıkları içeren hücrelerin boyanma yoğunluğunda artış gözlendi. Bununla birlikte, lipit damlacıkları içeren hücrelerin boyanma yoğunluğu diyabetik ratlara CoQ10 uygulanması ile azalmıştır.

Öneri: Bu sonuçlara göre, CoQ10 uygulamasının diyabetik ratların lipit anormalliklerini düzelttiği söylenebilir.

Anahtar kelimeler: Koenzim Q_{10}, diyabet, lipid profil, karaciğer, rat

Abstract

Aim: This research was carried out to evaluate the effects on lipid profile of Coenzyme Q_{10} in streptozotocin induced diabetic rats.

Materials and Methods: In the study, 38 adult male Wistar Abino rats were divided into five groups. Group I animals was no applied. Group II animals was intraperitoneally administered 0.3 ml corn oil daily and group III animals was intraperitoneally administered 10 mg/kg CoQ10 in 0.3 ml corn oil daily for four weeks. In group IV animals, diabetes was induced by subcutaneous injections of 40 mg/kg streptozotocin for two days as a single dose per day. In group V animals, diabetes was induced by same protocol applied to group IV and then these animals were intraperitoneally administered 10 mg/kg CoQ10 in 0.3 ml corn oil for four weeks. It was determined plasma triglyceride, total cholesterol, LDL, HDL, insulin and glucose levels in all groups. In liver sections, the staining intensity of hepatocytes containing lipid droplets were evaluated.

Results: Experimentally diabetes increased triglyceride, cholesterol and LDL levels, while these parameters decreased with CoQ10 treatment to diabetic rats when compared to diabetic group (P<0.05). Plasma HDL level was lower in diabetic group and plasma HDL level with CoQ10 treatment to diabetic rats increased to diabetic group (P<0.05). It was observed an increase in the staining intensity of hepatocytes containing lipid droplets in diabetes group. However, these staining intensity decreased by administration of CoQ10 to diabetic rats.

Conclusion: According to these results, it could be say that CoQ10 treatment recovered lipid abnormalities of diabetic rats.

Keywords: Coenzyme Q_{10}, diabetes, lipit profile, liver, rats

Introduction

Diabetes has been continuing to be a major health problem across the world as a complex disorder characterized by systemic complications (Rahimi et al. 2005). Atherosclerosis, retinopathy, nephropathy, and neuropathy are the complications caused by diabetes (Hussein et al. 2012, Hussein et al. 2013). In diabetes, there are substantial changes in vascular system associated with imbalances in carbohydrate, lipid and protein metabolism (Brownlee 2001). Oxidative stress and lack of tissue antioxidants are considered as a critical factor in etiology of numerous disorders (Długosz et al. 2004). Some previous studies indicated that oxidative stress arising from increasing of free radicals plays an important role in progress of disorders seen in diabetes (Hussein et al. 2012, Hussein et al. 2013). Oxidative stress develops as a result of inhibition of various enzymes and accumulation of harmful metabolic products by formation of hydroxyl radical, peroxy radical, superoxide anion, hydrogen peroxide, and free radicals (Giuglian et al. 1995, Modi et al. 2006). Negative changes occurring in lipid metabolism as well as carbohydrate metabolism in diabetic cases were revealed both experimentally and clinically (Rodrigues et al. 1986, Modi et al. 2006). It seems that there is a close correlation between hyperglycemia and plasma lipid abnormalities (Saudek and Eder 1979). Therefore, one of the disorders observed among complications caused by diabetes is cardiovascular diseases. It is reported that incidence of cardiovascular disease is 3-4 times higher in individuals with diabetes than those without diabetes. This increased prevalence of macrovascular and microvascular disorders in diabetes is suggested to be independent from pre-existing risk factors such as dyslipidemia, hypertension, and smoking. For this reason, diabetes is evaluated as a risk factor by itself for atherosclerosis. Oxidative stress plays an important role in atherogenesis by leading oxidation of low density lipoproteins (LDL). Oxide LDL, which recognized by the scavenger receptors on macrophages in addition to LDL receptors, causes formation of foam cells resulting in irregular cholesterol accumulation (Jialal et al. 2002, Rahimi et al. 2005).

Coenzyme Q10 (CoQ10) which is also known as ubiquinon 50, has significant functions in energy metabolism as a complementary part of electron transport system (Ernster and Dallner 1995). Functional group of CoQ10 which has lipophilic property due to long polyisoprene molecule is quinon chain. As an electron carrier in mitochondrial respiratory chain and mediating the reduction of quinon into quinol form, CoQ10 is involved in proton and electron transport through different membranes of cells and organelles. It is also important for other muscular tissues to function properly as well as heart muscle in particular (Crane 2001). CoQ10 which protects lipids, DNA, proteins, and other important molecules from oxidative damage and has the ability of synergic function with other antioxidants is defined as a strong systemic radical scavenger (Lass et al. 1999, Prosek et al. 2008). Some studies in which conducted experimentally diabetes was stated that CoQ10 had positive effects on plasma lipid profile and lipid peroxidation (Modi et al. 2006, Amin et al. 2014).

Based on mentioned information above, this study was designed with the belief that it will be beneficial to evaluate liver tissue as histologically and histochemically with the effects of CoQ10 administration on blood lipid profile of rats with streptozotocin induced diabetes.

Materials and Methods

In the present study, 38 adult, male, healthy Wistar Abino rats were used. The animals were divided into five groups and fed ad libitum with standard rat pellet for four weeks.

Group I (n=6): Nothing was applied.

Group II (n=6): 0.3 ml corn oil was intraperitoneally administered daily for four weeks.

Group III (n=6): 10 mg/kg CoQ10 (Sigma Aldrich, St. Louis, MO, USA) in 0.3 ml corn oil was intraperitoneally administered daily for four weeks.

Group IV (n=7): Diabetes was induced by subcutaneous injections of streptozotocin (Sigma Aldrich, St. Louis, MO, USA) at dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) for two days as a single daily dose per day.

Group V (n=9): Diabetes was induced by subcutaneous injections of streptozotocin at dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) for two days as a single daily dose per day and then CoQ10 in 0.3 ml corn oil was intraperitoneally administered at dose of 10 mg/kg to the rats with induced diabetes for four weeks.

The animals received 5% dextrose solution for next 3 days after 6h of streptozotocin administration to protect hypoglycemia. After 1 week from streptozotocin administration, the blood glucose levels were measured by using glucometer (PlusMED Accuro, Taiwan) via the tail vein to verify diabetes. Animals with blood glucose levels greater than 250 mg/dl were considered diabetic and were included in the experiment. Due to streptozotocin induced hypoglycemia, one animal from group V and three animals from group IV were died during the experiment. Blood samples were taken from all animals at the end of the four weeks. It was determined triglyceride, total cholesterol, LDL, HDL, insulin and glucose levels in the Abbott C8200 autoanalyzer using Abbott kits in the plasma samples. Tissue samples were taken from livers and fixed in formol calcium for 24 h at +4 °C. After fixation, liver samples were embedded in tissue freezing medium and 12 µm sections were cut using a cryostat. These sections

were stained with Sudan Black staining method. Then, sections were stained with nuclear fast red stain. All specimens were examined under light microscope (Leica DM2500, Germany) and were photographt by digital camera (Leica DFC 320). Intensity of hepatocytes containing lipid droplets was evaluated semi-quantitatively.

This study protocol was approved by Selcuk University Experimental Medicine Research and Application Center Ethics Committee (Report no. 2015-22).

Plasma lipid parameters, insulin and glucose levels in the study were statistically evaluated by using one-way ANOVA (SPSS 17). Differences among the groups were determined by Duncan's multiple range test. Mann-Whitney U test was used to compare data obtained from liver tissue. Differences were considered significant at $P<0.05$.

Results

In this study, the effect of CoQ10 on lipid profile in experimentally induced diabetic rats were summarized Table 1. Plasma insulin level in diabetic group was significantly lower than that of control group, while plasma glucose level was importantly higher than control group (Table 1, $P<0.05$). With CoQ10 application to diabetic rats, plasma insulin level significantly increased and plasma glucose level importantly decreased compared with diabetic group (Table 1, $P<0.05$). Experimentally induced diabetes resulted in significantly increments in total cholesterol, triglyceride and LDL levels, while these parameters statistically decreased with CoQ10 treatment to diabetic rats when compared to diabetic group (Table 1, $P<0.05$). Plasma HDL level was found to be importantly low in diabetic groups to control group and plasma HDL level with CoQ10 treatment significantly increased to diabetic group (Table 1, $P<0.05$).

It was observed an increase in the staining intensity of hepatocytes containing lipid droplets in the streptozotocin induced diabetes group (Figure 1B) compared to control, oil and CoQ10 groups (Figure 1A, 1B, 1C). However, these staining intensity decreased by administration of CoQ10 to diabetic rats (Figure 1D).

Discussions

Experimental and clinical trials indicate that there is a close correlation between hyperglycemia and plasma lipid abnormalities in diabetes (Saudek and Eder 1979, Rodrigues et al. 1986, Modi et al. 2006). In the study, while plasma triglyceride, total cholesterol and LDL levels of rats with experimentally induced diabetes increased significantly compared to values of control group (Table 1, $P<0.05$), plasma HDL level significantly decreased (Table 1, $P<0.05$). Hyperglycemia and increases in plasma triglyceride and cholesterol levels are prevalent in diabetes (Albrink et al. 1963, Sharma et al. 1970, Florey et al. 1973, Medalie et al. 1974). Events affecting lipid metabolism in diabetes have been tried to be explained with various mechanisms (Saudek and Eder 1979). The first one of these events is that insulin influences adipocytes to accelerate and increase triglyceride storage. Insulin was stated to decrease lipolysis of triglycerides by inhibiting hormone-sensitive lipase enzyme in adipocytes (Steinberg 1972, Fain 1973, Rodbell 1975). Secondly, it was suggested that insulin increased synthesis of VLDL-triglyceride in liver; thirdly increased clearance of peripheral triglyceride by stimulating lipoprotein lipase enzyme. Lipoprotein lipases is an enzyme system ensuring clearance of triglycerides from plasma lipoproteins rich in triglyceride such as VLDL and chylomicrons. As a matter of fact, major cause of hyperlipidemia in diabetes was suggested to be insufficient of triglyceride clearance by lipoprotein lipase (Saudek and Eder 1979). Fourthly, it was indicated that insulin stimulated hepatic 3-hydroxy-methylglutaryl-COA reductase (HMG-CoA reductase). HMG-CoA reductase is known as an enzyme limiting cholesterol synthesis rate. Lakshmanan et al. (1973) showed that HMG-CoA reductase activity decreased in rats with experimentally induced diabetes. Changes determined in plasma lipid levels of diabetic group in the study can be explained with the above mechanisms, which was consistent with significant decrease in insulin level in this group (Table 1, $P<0.05$). As similar to our results, it is stated that serum

Table 1. Effect of CoQ10 on plasma total cholesterol, triglyceride, HDL, LDL, insulin and glucose levels in streptozotocin induced diabetic rats (Mean±SE)

	T.Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Insulin (U/ml)	Glucose (mg/dl)
Group I	84.70±2.10^{c}	66.67±2.95^{c}	42.87±2.36^{ab}	25.24±1.47^{c}	22.73±0.98^{a}	86.57±3.49^{c}
Group II	86.08±2.26^{c}	68.58±2.19^{c}	41.83±2.29^{ab}	27.23±1.49^{c}	21.93±2.17^{a}	87.23±3.28^{c}
Group III	81.48±3.75^{c}	67.18±2.85^{c}	44.22±2.09^{a}	23.62±2.15^{c}	24.38±1.24^{a}	83.43±5.11^{c}
Group IV	124.96±3.07^{a}	104.79±3.35^{a}	27.74±1.56^{c}	69.73±2.24^{a}	13.89±1.16^{c}	357.19±22.78^{a}
Group V	98.69±1.89^{b}	83.29±3.37^{b}	37.43±1.24^{b}	41.39±1.27^{b}	18.04±1.11^{b}	203.49±11.37^{b}

$^{a-c}$The difference between mean values with different superscripts in the same column is significant at the $P<0.05$ level.
Group I, control; group II, oil; group III, CoQ10; group IV, diabetes; group V, CoQ10 and diabetes.

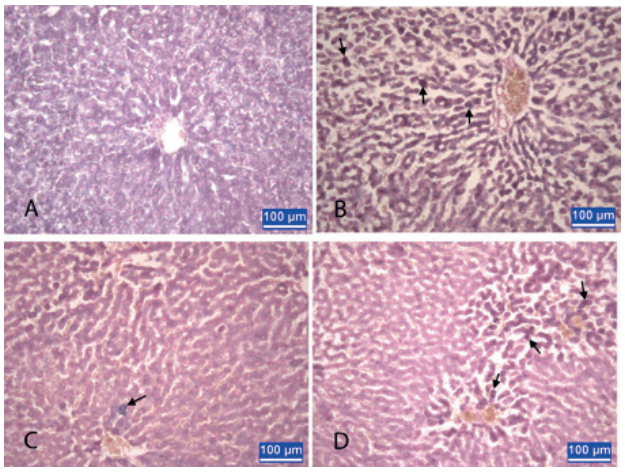

Figure 1. A: Liver tissue of control group rat. B: Liver tissue of diabetes group rat. C: Liver tissue of CoQ10 group rat. D: Liver tissue of CoQ10 + Diabetes group rat. Sudan Black staining

cholesterol, triglyceride, VLDL, and LDL levels were higher and HDL level was lower in diabetic animals compared to non-diabetic animals (Modi et al. 2006, Akah et al. 2009). It was reported that plasma triglyceride, cholesterol, free fatty acids and phospholipid levels also increased in experimental diabetes (Rodrigues et al. 1986). 30-40% of patients with diabetes were determined to have fasting hyperlipoproteinemia (New et al. 1963, Wilson et al. 1970, Hayes 1972, Kaufmann et al. 1975).

Based on significantly increased plasma insulin levels (Table 1, $P<0.05$) with CoQ10 treatment to diabetic animals compared to diabetic group in the study, plasma total cholesterol, triglyceride, and LDL levels significantly decreased (Table 1, $P<0.05$), whereas HDL level significantly increased (Table 1, $P<0.05$). Positive effects of CoQ10 determined on plasma lipid levels in this study support the results reported by some studies about the effects of CoQ10 administration on plasma cholesterol, triglyceride, and lipoproteins in rats with experimentally induced diabetes (Modi et al. 2006, Amin et al. 2014). The decrease determined in triglyceride level by administration of CoQ10 to diabetic rats in the study was suggested to be associated with the fact that CoQ10 increased LDL-specific antioxidant activity and cellular antioxidant capacity (Esterbauer et al. 1992, Lynch et al. 1994). The decrease in plasma total cholesterol level in the study could be assessed as a result of the decrease in LDL level and significant increases in HDL level caused by CoQ10 administration. Coenzyme Q10 application in healthy rats did not have a statistically significant effect on the determined parameters. This may be due to the absence of adverse reactions such as inflammatory reaction and oxidative stress in this group. Similarly, Kısmalı (2009) reported no significant change in some blood lipids, proteins and enzyme levels by addition of 10 mg/kg CoQ10 to healthy rats.

Liver, as an organ regulating blood-glucose level with some mechanisms such as gluconeogenesis, glycogenolysis and glycogenesis, is mostly affected by insulin-related changes, besides, it may be damaged considerably by oxidative stress. Güven et al. (2006) determined nuclear and cytoplasmic changes in hepataocytes in rats with streptozotocin induced diabetes. Doi et al. (1997) reported that hepatocytes in rats with streptozotocin induced diabetes have higher nuclear area compared to control group and boundaries of nuclei became also irregular.

Liver has important functions related to lipid metabolism such as synthesis and oxidation of fatty acids, formation of triglyceride from fatty acids, phospholipid synthesis and synthesis of lipoproteins. Hepatic lipidosis is accumulation of lipid in hepatocytes reflecting liver damage frequently. In this study, increment of lipid droplets in hepatocytes was remarkable in diabetic group. Lipid droplets in diabetic rats treated with CoQ10 was lower than compared to diabetes. The fact that the CoQ10 administration recovered the alterations in lipid contents in the hepatocytes caused by diabetes seemed to be consistent with positive effects of CoQ10 on plasma lipid fractions. These changes may be explained by its systemic antioxidant and LDL-specific antioxidant properties of CoQ10.

Conclusion

Consequently, it has been thought that the data obtained in the study were beneficial and important for further studies considering the positive effects of CoQ10 at this dose and these durations in diabetic animals.

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