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# RESEARCH ARTICLE

## A Study on Coenzyme Q10, experimentally induced diabetes and liver enzymes in rats

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## Ratlarda deneysel olarak oluşturulan diyabette CoQ10 uygulamasının karaciğer enzimleri üzerine etkilerine yönelik çalışma

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**Öz**

**Amaç:** Bu çalışmada deneysel olarak oluşturulan diyabette CoQ10 uygulamasının bazı karaciğer enzimleri üzerine etkilerinin belirlenmesi amaçlanmıştır.

**Gereç ve Yöntem:** Çalışmada bu amaçla 38 adet sağlıklı erkek Wistar Albino rat kullanıldı. Hayvanlar 5 gruba ayrıldı. Çalışmada dört hafta boyunca, grup 1 standart rat yemi ile beslenirken, grup 2'deki hayvanlara bu yeme ilaveten intraperitoneal (IP) olarak 0,3 ml mısır yağı ve grup 3'deki hayvanlara aynı yeme ilaveten IP olarak günde 10 mg/kg CoQ10 uygulaması yapıldı. Grup 4'deki hayvanlarda 40 mg/kg dozunda 0.1 M sitrat buffer (pH 4.5) içerisinde streptozotosinin günde tek doz olmak üzere iki kere subkutan (SC) enjeksiyonuyla deneysel diyabet oluşturuldu. Grup 5'deki hayvanlarda 40 mg/kg dozunda 0.1 M sitrat buffer (pH 4.5) içerisinde streptozotosinin günde tek doz olmak üzere iki kere SC enjeksiyonuyla deneysel diyabet oluşturuldu ve sonra dört hafta boyunca IP olarak günde 10 mg/kg CoQ10 uygulaması yapıldı. Dördüncü haftanın sonunda bütün hayvanlardan kan örnekleri alındı. Bu plazma örneklerinde, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), alkalin fosfataz (ALP) ve γ-glutamil transpeptidaz (GGT) düzeyleri belirlendi.

**Bulgular:** Çalışmada diyabet oluşturulan grupta AST, ALT, ALP ve GGT düzeyleri kontrol grubuna göre önemli artışlar ($P<0.05$) gösterdi. Diyabet oluşturulan hayvanlara CoQ10 uygulaması ile birlikte bu enzim düzeylerinde diyabet grubu ile karşılaştırıldığında önemli azalmalar ($P<0.05$) gözlendi.

**Öneri:** Sonuç olarak, CoQ10 uygulamasının diyabetin zararlı etkileri sonucu oluşan karaciğer hasarı üzerine yararlı olabileceği düşünülmektedir.

**Anahtar kelimeler:** Koenzim Q10, diyabet, karaciğer enzimleri, rat

**Abstract**

**Aim:** This study was conducted to determine the effects of CoQ10 supplementation on some liver enzymes in diabetes status.

**Materials and Methods:** In the study, 38 healthy male Wistar Albino rats were used. The rats were divided into five groups. The animals in group 1, group 2 and group 3 were received standard diet, standard diet plus IP 0,3 ml corn oil and standard diet plus IP 10 mg/kg CoQ10 for four weeks, respectively. In group 4, diabetes was performed via SC injections of Streptozotocin (STZ) at dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) single daily dose for two days. In group 5, diabetes was made via SC injections of STZ at a dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) single daily dose for two days and then received IP 10 mg/kg CoQ10 for four weeks. At the end of the fourth week, blood samples were taken from all animals. In plasma samples, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GGT) levels were determined.

**Results:** In this study, AST, ALT, ALP and GGT levels in diabetic group significantly increased compared with control group levels ($P<0.05$). CoQ10 application to diabetic animals significantly reduced these enzymes levels compared to diabetic group ($P<0.05$).

**Conclusion:** In conclusion, it is thought that CoQ10 supplementation may be beneficial on liver damage resulting from hazardous effects of diabetes.

**Keywords:** Coenzyme Q10, diabetes, liver enzymes, rat

## Introduction

Diabetes mellitus is the most common life-threatening metabolic disorder. One of the five diseases leading death in the world is diabetes mellitus (Gipsen and Biessels 2000, Chandramohan et al. 2008). In the fasting and postprandial states, normal blood glucose concentration is regulated by the liver. Insulin deficiency result in glycogenolysis and increased glucose production in liver (Harris 2005).

Liver function tests are commonly used in clinical practice to observe liver diseases, to follow the progression of any disease and the effects of potentially hepatotoxic drugs. The serum aminotransferases, alkaline phosphatase, bilirubin, albumin and prothrombin time are the most measured parameters in liver function tests. Aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), reflect the concentration of intracellular hepatic enzymes that have leaked into the circulation and these enzymes are regarded as markers of hepatocyte injury. On the other hand, alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT) and bilirubin serve as markers of biliary function and cholestasis. Albumin and prothrombin levels show hepatic synthesis capacity. In acute viral hepatitis, ischemic hepatitis, drug- or toxin-induced liver injury, aminotransferases may increase greater than eight-fold of normal limit (Harris 2005).

Coenzyme Q10 (CoQ10) or ubiquinone is known a lipid-soluble and vitamin-like compound and play important role in the mitochondrial respiratory chain as well as a natural scavenger of free radicals (Franke et al. 2010, Asker 2011, Alam and Rahman 2014). Although CoQ10 is synthesized by cells of the body, current studies reported that CoQ10 supplementation may be beneficial for improving and preventing pathological conditions such as metabolic syndrome, hypertension, diabetes, liver diseases, and insulin resistance (Moazen et al. 2013, Alam and Rahman 2014, Farsi et al. 2016).

In this study, our aim was to determine the effect of CoQ10 supplementation on some liver enzymes in experimentally induced diabetic rats.

## Materials and Methods

In the study, 38 healthy male Wistar Albino rats were used. The animals were kept in individual cages for the four weeks. The animals were allowed free received to water and standard pellets. The rats were divided into five groups. The mean weights of all groups were similar.

Group 1 (n=6): standard rat pellets for four weeks.
Group 2 (n=6): 0,3 ml corn oil IP daily for four weeks.
Group 3 (n=6): IP with 10 mg/kg CoQ10 (Sigma-Aldrich, St. Louis, MO, USA) daily for four weeks.
Group 4 (n=7): SC injections of STZ (Sigma-Aldrich, St. Louis, MO, USA) at a dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) single daily dose for two days.
Group 5 (n=9): SC injections of STZ (Sigma-Aldrich, St. Louis, MO, USA) at a dose of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) single daily dose for two days and IP with 10 mg/kg CoQ10 daily for four weeks.

Diabetes was performed with streptozotocin (STZ) by SC injection at a dose of 40 mg/kg daily in 0.1 M citrate buffer (pH 4.5) single daily dose for two days. To prevent the STZ-induced hypoglycemia, rats received %5 dextrose solution after 6 h of STZ administration for next 3 days. After 1 week STZ injections, diabetes was verified by measuring blood glucose level strips using glucometer (PlusMED Accuro, Taiwan) via the tail vein. Animals having a blood glucose level higher than 250 mg/dL were accepted as diabetic and were taken into the experiment. During the experiment, three animals from group 4 and one animal from group 5 were dead due to STZ-induced hypoglycemia. At the end of the study, blood samples were taken from all animals. In plasma samples, AST, ALT, ALP, GGT levels were determined in an Abbott-C8200 autoanalyser using Abbott kits. The Ethical Committee of Selcuk University Experimental Medicine Research and Application Center (Report no. 2015-50) approved the study protocol.

The data were analyzed using one-way ANOVA (SPSS 17). Differences among the groups were determined by Duncan's

Table 1. Effects of CoQ10 on AST, ALT, ALP and GGT levels (Mean±SE)

| Groups | AST | ALT | ALP | GGT |
|---|---|---|---|---|
| | U/L | U/L | U/L | U/L |
| Group 1 | 96.52±6.95$^{c}$ | 19.12±1.50$^{c}$ | 64.13±7.30$^{c}$ | 6.85±1.01$^{c}$ |
| Group 2 | 104.25±7.03$^{c}$ | 21.53±2.13$^{c}$ | 64.57±6.40$^{c}$ | 7.17±1.17$^{c}$ |
| Group 3 | 91.35±4.44$^{c}$ | 17.72±1.88c | 59.80±3.95$^{c}$ | 6.78±1.10$^{c}$ |
| Group 4 | 179.26±8.27$^{a}$ | 38.89±3.27$^{a}$ | 98.86±5.19$^{a}$ | 17.61±1.71$^{a}$ |
| Group 5 | 145.01±7.59$^{b}$ | 29.87±3.23$^{b}$ | 82.09±5.27$^{b}$ | 12.43±1.26$^{b}$ |

The difference between mean values with different superscripts in the same column is significant for each parameter, P<0.05.

multiple range test. Differences were considered significant at P<0.05.

## Results

At the end of the study, AST, ALT, ALP and GGT levels in rats were presented in Table 1. In this study, AST, ALT, ALP and GGT levels in the diabetic group significantly increased compared with control group levels (P<0.05, Table 1). CoQ10 application to diabetic animals significantly reduced these enzyme levels compared to diabetic group (P<0.05, Table 1). In this study, there are no differences among control, oil and CoQ10 groups regarding to AST, ALT, ALP and GGT levels.

## Discussion

The liver plays an important role in detoxification and excretion of destructive agents in body intoxication (Esfahani et al. 2013). Liver enzymes include AST, ALT, ALP and GGT used as markers for liver damage. High enzyme levels are indicator of the fatigue and damage occurred in big tissue structures such as liver and skeletal muscle (Demirci 2015). In experimentally induced diabetic rats, it was noted that these enzymes were increased compared to healthy rats (Al-Ghaithi et al. 2004, Chandramohan et al. 2008). In diabetes, it was suggested that abnormal hepatocellular function is related with insulin resistance and high levels of hepatic enzymes are associated with development of diabetes (Ohlson et al. 1988, Perry et al. 1998, Vozarova et al. 2002). However, it was reported that streptozotocin has hepatotoxic effect by increasing the plasma level of many liver enzymes (Al-Ghaithi et al. 2004, Chandramohan et al. 2008). It has also been noted the presence of liver steatosis in patients with diabetes (Kelley et al. 2003, Bulum et al. 2011). Clark et al. (2003) found higher serum markers of liver damage, including AST, ALT and ALP in the fatty liver subject. Vozarova et al. (2002) also reported that fatty change in liver depending on diabetes may reflect inflammation and cause concomitant elevation of liver markers. Diabetic patients have impairment glycogen synthesis due to defective activation of glycogen synthase in the liver (Ferrannini et al. 1990). There is an excess glycogen accumulation in the liver of 80% of diabetic patients (Stone and Van Thiel 1985). It was reported that excessive glycogen deposition may exhibit hepatomegaly and liver enzyme abnormalities (Chatila and West 1996, Levinthal and Tavill 1999). The obtained results in this study are consistent with the above data. In our study, the increases in hepatic markers may result from both developments of diabetes and hepatotoxic effect of streptozotocin.

CoQ10 was widely used as therapeutic and supplementary agent due to the antioxidant, antiinflamatory and antiapoptotic effects (Esfahani et al. 2013). In this study, CoQ10 application in diabetic rats showed important decreases (P<0.05, Table 1) in the obtained enzyme levels compared to diabetic animals. These effects of CoQ10 were attributed to inhibition of apoptosis in hepatocytes and attenuating oxidative stress and inflammation through decreasing cyclooxygenase activity (Vasiliev et al. 2011, Fouad and Jresat 2012). In our study, it was suggested that administration of CoQ10 may alleviate liver damage resulting from experimentally induced diabetes. There are limited experimental studies that evaluated the effects of CoQ10 on liver function and diabetes. It has been noted that CoQ10 supplementation improves the life span of rats receiving a diet consist of high level polyunsaturated fatty acids (Quiles et al. 2004, Quiles et al. 2005, Hashemi et al. 2008). Bello et al. (2005) reported that CoQ10 addition to diet protected liver cell membranes from oxidative effects in rats. Similarly, it has been suggested that CoQ10 defends liver tissue against toxic effects of ochratoxin A (Sutken et al. 2007). Esfahani et al. (2013) found the important decreases in AST, ALT and ALP levels in rats received CoQ10 compared to control group. In accord to the above studies, the decreases in enzyme levels with CoQ10 application to diabetic rats in this study seem to be logical.

## Conclusion

As a result, CoQ10 supplementation may be beneficial on liver damage resulting from hazardous effects of diabetes. Nevertheless, further studies are needed to put forth the effects of CoQ10 on liver function in some metabolic disorders such as diabetes.

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