Effect of Diabetes, Hyperlipidemia and Atherosclerosis on Human Plasma Coenzyme Q10 Concentration

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Abstract: Coenzyme Q10 (CoQ10) is a powerful lipid-soluble antioxidant, which is considered as an important cofactor in the mitochondrial electron transfer pathway. There is a possible relationship between CoQ10 and the pathogenesis of type 2 diabetes, hyperlipidemia, and atherosclerosis. This study aimed to assess the effects of these diseases on human plasma CoQ10 concentration. A total of 200 human male and female subjects with ages of 20-70 years were divided into four groups: normal control subjects, diabetic type 2 patients, hyperlipidemic patients and patients with atherosclerosis. The samples of each group were comprised of 25 males and 25 females. The mean concentration of plasma coenzyme Q10 was close to each other in male and female healthy subjects (0.21 µM vs. 0.19 µM, respectively). It was found that the concentration of plasma CoQ10 was decreased in both male and female patients as compared with the control subjects. These changes could be attributed to the increased production of reactive oxygen species and decreased antioxidant concentrations. There is significant correlation between low CoQ10 levels and diabetes, hyperlipidemia and atherosclerosis, this correlation does not necessarily indicate a causal relationship.

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1. Introduction

Coenzyme Q10 (also known as 2, 3-dimethoxy-5-methylbenzoquinone, ubiquinone, ubidecarenone, mitoquinone, vitamin Q10, CoQ10, or Q10) belongs to the family of ubiquinone. Ubiquinone refers to the ubiquitous occurrence of these compounds in living organisms and their chemical structure. CoQ10 is a benzoquinone compound, where the "Q" refers to the quinone chemical group and the "10" to the 10 iso-prenyl chemical subunits. The term "coenzyme" is indicated as an organic non-protein component. Depending on the organism, the length of the side-chain varies from 6 to 10 (Figure 1). The ubiquinone found in human has a benzoquinone head and a tail of 10 isoprene units (a total of 50 carbon atoms) [1-3].

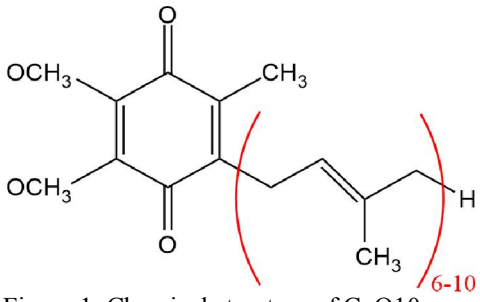

Figure 1. Chemical structure of CoQ10

CoQ10 is a lipid-soluble endogenous antioxidant. Its absorption occurs slowly depending on the presence of fat in the gastrointestinal tract. It is initially sequestered by chylomicrons and distributed to the liver to be incorporated into very low density lipoproteins (VLDL). The excretion of CoQ10 primarily occurs through the biliary tract [6]. It is naturally synthesized in human body; therefore, it is not a vitamin. It is referred as "vitamin-like" substance as it closely resembles vitamin E. CoQ10 is present in most tissues mostly as ubiquinol, and plays important role in the mitochondrial electron transport chain, which regulates oxidative phosphorylation [5]. In mitochondria, the cellular machinery is driven by the energy, generated through the conversion of carbohydrates and fats into ATP. In diabetes, hyperlipidemia, and atherosclerosis, the concentrations of CoQ10 is decreased due to reduction of mitochondrial oxidative phosphorylation which decreases the ATP production. Moreover, in assessing the process of electron transfer during oxidative phosphorylation, the inhibition of certain enzymes by CoQ10 leads to generation of free radicals that creates oxidative stress [34].

The highest concentrations of CoQ10 are found in tissues that require high energy such as liver,

kidney, heart, and pancreas. The minimum concentration of CoQ10 is present in the lungs [7-9]. CoQ10 is present in all membranes as an antioxidant by inhibiting initiation and propagation of lipid and protein oxidation [4]. However, majority of the people have a dietary intake of less than 10 mg/day of CoQ10, which is not enough to achieve therapeutic effects. Previous study showed that CoQ10 levels decline gradually with age, due to increased requirements, reduced production, or insufficient intake of the chemical precursors needed for synthesis [10]. The production of CoQ10 may also decrease due to deficiency of specific nutrients, any disease, or certain drugs [11]. Therefore, oral supplements of CoQ10 are known to elevate plasma and lipoprotein concentrations of CoQ10 in human [12, 13]. Recent studies reported that CoQ10 prevents the development of diabetic nephropathy, neuropathy, and cardiomyopathy in diabetic mice [14, 15].

Reactive Oxygen Species (ROS) are generated during normal cellular function. ROS are termed as transient species due to their high chemical reactivity. The main source of ROS generation is mitochondria, and it leads to oxidation of DNA, proteins, and lipid. Complexes I and III are the main sites of superoxide radical generation in the respiratory chain. ROS releases in the matrix and the inter-membrane space. When ROS production is increased to an extent to overcome the cellular antioxidants, it creates oxidative stress. Antioxidants are molecules that decreases the oxidation of cellular substrates by scavenging free radicals or activating detoxifying/defensive proteins. The ROS produced in mitochondria contribute to cell damage, leading to pathological conditions [16, 17]. The ROS is controlled by the antioxidant defense. The increased generation of ROS during oxidative stress may cause type 2 diabetes, hyperlipidemia, and atherosclerosis.

CoQ10 is regarded as an effective lipophilic anti-oxidant present in almost all human tissues. Therefore, the present study was conducted to assess the level of CoQ10 in human plasma between healthy individuals and patients with type 2 diabetes, hyperlipidemia and atherosclerosis. However, the main objective is to provide an ovierview of the impact of these three diseases on CoQ10 levels in the same study under the same conditions. Moreover, it is important to find the link between the lipid profile and the CoQ10 levels between different sexes in different diseases. Hence, the study aims to investigate possible correlation between plasma CoQ10 concentrations along with various biochemical blood analytes in males and females subjects. The various blood analytes include plasma glucose, plasma total cholesterol, plasma trigacylglycerol (TAG), plasma HDL-cholesterol, and plasma LDL-cholesterol with normal healthy adult subjects and patients with diabetes type 2, hyperlipidemia, and atherosclerosis.

2. Material and Methods

All the kits needed to conduct this study were obtained from Biosystems (S.A. Costa Brava 30, Barcelona Spain). Reagent kits included glucose, cholesterol, triacylglycerol, HDL-cholesterol and LDL-cholesterol. CoQ10 and benzoquinone were purchased from Sigma (Taufkirchen, Germany). Methanol, ehanol, and n-propanol were obtained from BDH chemicals, Pole, Dourets, UK. Chemistry parameters were analyzed by spectrophotometry (Jenway, model 6305, UK). The concentration of CoQ10 was determined by high-performance liquid chromatography (HPLC) with UV detection.

1.1. Sample collection

A total of 200 subjects (100 males and 100 females) were recruited in this study. These subjects were divided into 4 groups as follow:

1. Normal control subjects: 25 females and 25 males.
2. Type 2 diabetic patients: 25 females and 25 males.
3. Hyperlipidemic patients: 25 females and 25 males.
4. Patients with atherosclerosis, selected from the cardiac care unit (CCU): 25 females and 25 males.

Healthy individuals suffering no major illness and used no medication were used as a control group. On contrary, patients' samples were collected during their routinely visits to the patients clinics or admitted to CCU at King Abdulaziz University Hospital (Jeddah- SA). The main criteria to select diabetic patients was having a fasting blood glucose above 126 mg/dl after at least eight hours without eating. To select hyperlipidemia patients, the blood levels of any or all lipids must be above the normal range after fasting for at least 12 hours. Patients with atherosclerosis were diagnosed and selected based on test results (e.g. blood sugar and cholesterol), medical and family histories. Samples collection from the patients were done according to the ethical rules approved by King Abdulaziz University.

The weight and height of all subjects were recorded to calculate the body mass index (BMI) (weight/height^2). Venous blood samples were collected in the lithium heparin tubes. Plasma samples were separated from blood by centrifugation at 3000 g for 10 minutes and stored at -20°C. The plasma samples were used to carry out the assay for CoQ10, glucose, cholesterol, TAG, HDL-cholesterol, and LDL-cholesterol.

1.2. Determination of clinical parameters

Fasting plasma levels of glucose, cholesterol, TAG, HDL- cholesterol, and LDL- cholesterol were

determined by enzymatic analyses using commercial kits and following the manufacture instructions.

1.3. Determination of plasma CoQ10

Determination of CoQ10 was based on the method suggested by Mosca et al. [18]. The methods involved the oxidation of CoQ10 in the sample by treating it with para-benzoquinone followed by extraction of 1-propanol and injecting into the HPLC apparatus. The separation was performed on a reversed-phase Supelcosil LC18 column and UV detection was performed at 275 nm. This method helped to achieve a linear detector response for peak area measurements over the concentration range of 0.05 – 3.47 μM. The standard curve was constructed using propanol/water solutions of pure CoQ10.

1.4. Statistical analysis of data

Statistical analysis of data was performed using Statistical Package of Social Sciences, (SPSS version 14.0 for windows and Microsoft EXCEL, version 2003 for windows). The data were expressed as means ±.

(ANOVA) was used to analyze the obtained data. Post Hoc test procedure was conducted using the Bonferroni between groups following a significant ANOVA test when the values of the measured parameters are normally distributed. Kruskal–Wallis test was used to study the difference between groups when the value of the measurement parameters is not distributed normally.

3. Results

A total of 200 subjects (100 females and 100 males) were grouped in four categories; control group, diabetes mellitus group, hyperlipidemia group, and atherosclerosis group. The anthropometric and metabolic characteristics of control and patient subjects are summarized in table 1. The mean age of all female patients was significantly elevated as compared to healthy individuals. While the mean age of male patients with atherosclerosis was significantly elevated (22.8%, p<0.0001). However, as compared to the control group, the body mass index of male and female diabetic, hyperlipidemic, and atherosclerosis patients was significantly increased.

Table 1. Age and body mass index (BMI) of female and male individuals of different group

Group	Age (years)		BMI (kg/m^2)	
	Females	Males	Females	Males
Control	36.3±12.1	44.3±12.7	24.2±3.0	25.9±2.0
Diabetics	55.6±12.4*	52.3±11.1	28.6±4.4*	30.3±3.4*
Hyperlipidemia	52.4±11.4*	51.6±11.6	29.7±5.1*	30.4±3.8*
Atherosclerosis	58.6±10.4*	54.4±09.9*	27.3±4.5*	28.8±2.7*

Results are expressed as means ± SD. Significant differences between control and all other groups were made by one way ANOVA (* $p < 0.0001$) where total number of samples for each group was 25.

There was significant decrease in the plasma CoQ10 concentrations between female control subjects and patients (Table 2). The plasma glucose concentration was the highest in the diabetic group (74.6%, p<0.0001) as compared with other groups; whereas, the lowest concentration of plasma total cholesterol was observed in patients with atherosclerosis (19.3%, p<0.0001) compared to other patients groups. The plasma concentrations of HDL-cholesterol and TAG were close to each other with no significant differences between the different groups. As compared with the control group, plasma LDL-cholesterol concentration was significantly elevated in both diabetic (39.5%, p<0.0001) and hyperlipidemic (47.5%, p<0.0001) individuals.

In control, diabetic, hyperlipidemic, and atherosclerosis male subjects, there was no significant difference of plasma CoQ10 concentrations among the male subjects (Table 3).

Table 2. Plasma coenzyme Q_{10} and biochemical parameters concentrations of female subjects

Group	Glucose (mg/dl)	Total Cholesterol (mg/dl)	HDL - C (mg/dl)	LDL - C (mg/dl)	Triacylglycerol (mg/dl)	CoQ_{10} (μM)
Control	100.5±12.3	165.7 ± 35.9	53.6±14.8	95.2 ± 12.2	141.4 ± 48.5	0.19 ± 0.04
Diabetics	175.5±90.3*	200.8±34.5	43.5±16.7	132.8±34.1*	198.8 ± 78.5	0.16± 0.11 *
Hyperlipidemia	169.8±115.1*	223.2 ± 29.0	41.9±49.1	140.4±35.8*	235.2 ± 81.5	0.18± 0.09 *
Atherosclerosis	160.1±127.9*	197.7±38.1*	42.9±18.1	126.6 ± 33.8	161.0 ± 55.3	0.13± 0.10 *

Results are expressed as means ± SD. Significant differences between control and all other groups were made by one way ANOVA for normally distributed data (Total Cholesterol & LDL) and the others were made by Krwskwallis test (* $p < 0.0001$) where total number of samples for each group was 25.

Table 3. Plasma coenzyme Q_{10} and biochemical parameters concentrations of male subjects

Group	Glucose (mg/dl)	Total Cholesterol (mg/dl)	HDL – C (mg/dl)	LDL – C (mg/dl)	Triacylglycerol (mg/dl)	CoQ_{10} (μM)
Control	95.3±8.3	171.7± 34.6	45.2±10.9	102.3±16.50	136.4 ± 36.8	0.21±0.08
Diabetics	188.1±75.3*	209.8±30.3 *	38.8±13.7	126.7±24.4*	218.3 ± 96.2	0.15±0.07
Hyperlipidemia	168.5± 84.2*	214.2±41.1	36.3±15.5	130.2±39.0*	247.3 ± 95.5	0.15±0.32
Atherosclerosis	158.4±112.7*	193.7±33.4 *	37.6±18.7	121.3±30.7	169.8 ± 72.9	0.13±0.05

Results are expressed as means ± SD. Significant differences between control and all other groups were made by one way ANOVA for normally distributed data (Total Cholesterol, LDL & TG) and the others were made by Krwskwallis test (* $p < 0.0001$) where total number of samples for each group was 25.

The total plasma concentration of cholesterol was higher in all patient groups, as compared to the control group. Contrary to control group, all patient subjects have significant elevation in plasma glucose level. The HDL-cholesterol and TAG concentrations of male patients were close to the control group. The plasma concentration of LDL-cholesterol was significantly elevated in diabetic and hyperlipidemic males as compared with the control group (19.3%, $p<0.0001$ vs. 27.3%, $p<0.0001$, respectively). The correlation between CoQ10 and biochemical parameters in female and male subjects are represented in table 4.

In females, there was no significant correlation in all cases; whereas, TAG in control group had a positive correlation with CoQ10. The cholesterol levels were closely associated with CoQ10 (0.304) in diabetic patients and HDL-cholesterol levels in patients with atherosclerosis (0.243). On the contrary, the correlation between CoQ10 and biochemical parameters in male subjects presented positive correlations with total cholesterol (0.397) and LDL-cholesterol (0.426) in control group. Likewise, TAG was positively correlated with CoQ10 in diabetic group (0.449). There was no significant correlation observed between CoQ10 and other parameters in patients suffering hyperlipidemia and atherosclerosis.

4. Discussions

This study aimed to find a possible relationship between CoQ10 and the pathogenesis of type 2 diabetes, hyperlipidemia, and atherosclerosis. The results indicated that the mean concentration of plasma CoQ10 in control male is 0.21 μM and in female subjects is 0.19 μM. The results are consistent with the findings of the study conducted by Mosca et al. [18], who investigated that plasma CoQ10 concentrations were between 0.05 - 3.47 μM. However, there was remarkable decrease in the CoQ10 levels in male and female patients. These changes were significant among the female patients as compared to the the male individuals (Figure 2). Healthy females have lower CoQ10 levels than males while diabetic and hyperlipidemic females have higher concentrations than males. It is possible that different sexes and sex hormones may contribute to lower levels of CoQ10 in diseases.

Table 4: The correlation between CoQ10 concentration and biochemical parameters in female and male subjects.

	Females				Males			
	Control	Diabetes	Hyperlipidemia	Atherosclerosis	Control	Diabetes	Hyperlipidemia	Atherosclerosis
Glucose (mg/dl)	0.107	- 0.039	0.009	- 0.063	0.024	- 0.010	- 0.145	- 0.113
Cholesterol (mg/dl)	0.258	0.304	0.113	0.121	0.397*	0.205	0.328	0.256
TAG (mg/dl)	0.417*	0.169	0.217	0.161	- 0.030	0.449 *	0.307	0.178
LDL-C (mg/dl)	0.199	0.035	0.021	- 0.027	0.426*	- 0.021	0.106	0.143
HDL-C (mg/dl)	- 0.262	- 0.257	- 0.073	0.243	0.090	0.107	0.113	- 0.101

* Correlation is significant at the 0.05.

Yalcin et al (2004) [19] reported that the antioxidant functioning of the reduced form of CoQ10 had a protective effect against atherosclerosis. Altered oxygen utilization and increased formation of ROS contributes to atherogenesis. CoQ10 levels have been reported to be either low or high in type 2 diabetes as compared to healthy individuals. The lower level of CoQ10 in diabetic patients is indicated by the increased production of ROS [20, 21]. In the study, the lower levels of CoQ10 in subjects with type 2 diabetes and hyperlipidemia are due to increased generation of ROS and decreased antioxidant concentrations. The increased generation of ROS and decreased antioxidant concentrations may result due to abnormalities in carbohydrates and lipid metabolism [22, 23]. Higher level of glucose induces oxidative stress while elevated formation of ROS can

cause oxidative damage to cellular constituents, such as DNA, lipids and proteins [24, 25].

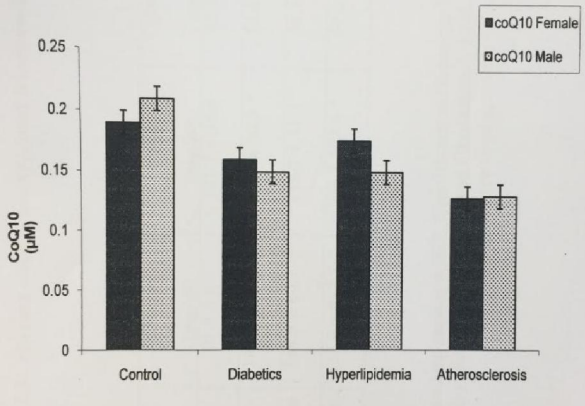

Figure 2. A histogram showing the mean coenzyme Q10 of control, diabetic, hyperlipidemic, and atherosclerosis patients in males and females

It is known that the age and BMI have an effect on CoQ10 levels. In this study, we focused on adults subjects. The body generates less CoQ10 as getting older, therefore, the comparison was between age-matched control and patients groups. Moreover, CoQ10 helps to inhibit the increase on body fat but in this study the correlation between healthy and patients groups were significant in all groups (males and females) which may confirm that the reduction in CoQ10 levels were due to diseases. Indeed, BMI was elevated in both male and female cases with significant change ($p<0.0001$). These results are supported by few other studies that indicated that the prevalence of diabetes mellitus and hyperlipidemia usually increases with increased BMI [26, 27]. Increased body weight and BMI are considered as a risk factor for development of atherosclerosis. Al-Bazi et al (2011) indicated that as compared to males, the adverse effects of smoking were higher in females due to reduced plasma levels of CoQ10, total cholesterol, HDL-cholesterol, and abnormal atherogenicity indices [28].

The plasma lipid concentrations were significantly increased in all cases when compared with the control group. In diabetic and hyperlipidemic females, the plasma levels of LDL-cholesterol were increased by 39.5% and 47.5% respectively. The plasma levels of LDL-cholesterol in patients with atherosclerosis were not significantly altered. Moreover, as compared with the normal control, higher amounts of TAG and total cholesterol were seen in all cases. The plasma HDL-cholesterol concentration was lower in the patients suffering diabetes, hyperlipidemia, and atherosclerosis with no significant change, which is consistent with the previous researches [29-31].

The increased concentration of plasma cholesterol among patients is probably due to the increase in DL-cholesterol fractions. The increase in this fraction is ascribed to an increase in the IDL-cholesterol fraction. The higher levels of IDL-cholesterol and LDL-cholesterol are associated with increased vascular risk [29]. The high plasma TAG concentration is attributed to an increase in the production of VLDL, decreased conversion of VLDL to LDL, and impaired LDL clearance [32]. There are beneficial effects of oral supplements of CoQ10 on disease progression and oxidant status in patients with type 1 and 2 diabetes. It was proved that 12 weeks CoQ10 treatment (100 mg twice daily) induced positive effects on the extracellular redox balance, lipid profile, and metabolic control [33].

The present study has emphasized on the therapeutic potential of CoQ10 indicating that a correlation exists between low CoQ10 levels and diabetes, hyperlipidemia and atherosclerosis. It has been concluded that the oxidative stress is elevated among the patients suffering diabetes type 2, hyperlipidemia, and atherosclerosis that is determined by decreased plasma concentration of CoQ10. The free radicals generated as a result of oxidative stress, which cannot be neutralized by the endogenous antioxidant response resulting in cardiovascular, nerve and endothelial dysfunction. The complication of diabetes, hyperlipidemia, and atherosclerosis can be prevented by supplementation of CoQ10. In the future, we aim to correlate between CoQ10 concentrations and sex hormones to clarify whether gender differences affect CoQ10 concentrations in these diseases.

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