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Effects of Coenzyme Q10 Administration on Glucose Homeostasis Parameters in Prediabetic Patients

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Abstract

Background: Prediabetes or "intermediate hyperglycemia" is determined on the bases of glycemic parameters which are above normal but below diabetic thresholds . Prediabetes is associated with the presence of insulin resistance and β-cells dysfunction . Coenzyme Q_{10} is well located in membranes in close proximity to the unsaturated lipid chains to act as a primary scavenger of free radicals. Since much of the coenzyme Q_{10} in cell membranes is in the quinol form , it can be a very effective antioxidant. Even more important is the presence of enzymes in all membranes which can reduce any coenzyme Q_{10} quinone radical generated by reaction with lipid or oxygen radicals. The target of this study was to evaluate the effects of coenzyme Q10 administration on glucose homeostasis parameters in prediabetic patients.

Methods: this study included, 25 patients treated with dietary control and life style modifications for 12 weeks, 25 patients treated with Q_{10} (200mg) plus dietary control and life style modifications for 12 weeks. To have an idea about the normal values of study parameters and in order to assess how much the drug used in the study were able to normalize the abnormal parameters, other 20 in addition to 50 patients.

Results: Coenzyme Q_{10} demonstrated a significant decrease in the F.B.S, HbA1c , Fasting Insulin and Insulin resistance at the end of 12 weeks ($P<0.05$) compared with baseline measurements.

Conclusion: The results of the study showed that coenzyme Q_{10} has an effective effect on glycemic control.

Key words: Prediabetes , Coenzyme Q_{10} , glycemic control.

INTRODUCTION

Prediabetes or "intermediate hyperglycemia" is determined on the bases of glycemic parameters which are above normal but below diabetes thresholds. It is a high risk state for diabetes with an estimated annual conversion rate of 5%–10%; a similar proportion is converting back to normoglycemia (1). Prediabetes is associated with the presence of insulin resistance and β-cell dysfunction. These abnormalitiesstart before glucose changes are detectable(2).

The high risk for developing diabetes is related to two states; impaired fasting glucose-IFG (defined as fasting plasma glucose of 6.1–6.9 mmol/L in the absence of impaired glucose tolerance - IGT), and to IGT (defined as post-load plasma glucose of 7.8–11.0 mmol/L based on 2-hour oral glucose tolerance test (OGTT) or a combination of both (3). A lower cut-off value for IFG (FPG 5.6–6.9 mmol/L) is employed by the American Diabetes Association. In addition, it has introduced hemoglobin A1c levels of 5.7–6.4% as a parameter of high diabetes risk(4).Combination of IFG and IGT marks a more advanced disturbance of glycemic homeostasis (5).

The central mechanism that is responsible for risks in prediabetes is endothelial dysfunction due to the elevated formation of reactive oxygen species (ROS) and advanced glycation end products (AGEs) as well as increased lipid peroxidation under hyperglycaemic conditions (6).

Coenzyme Q10, known as ubiquinone, , and abbreviated at times to CoQ10, Q10, where Q refers to the quinone chemical group, and 10 refers to the number of isoprenyl chemical subunits in its tail. This oil-soluble, vitamin-like substance is present in most eukaryotic cells, primarily in the mitochondria. It is a component of the electron transport chain and participates in aerobic cellular respiration, generating energy in the form of ATP (7). Coenzyme Q10 is well located in membranes in close proximity to the unsaturated lipid chains to act as a primary scavenger of free radicals. Since much of the coenzyme Q10 in cell membranes is in the quinol form , it can be a very effective antioxidant (8).

MATERIAL AND METHODS

Study design: The current study was conducted on 50 Prediabetic patients (31 males, 19 females) their ages from 30-65 year were seen in Al-Sader Teaching Hospital. The patients were diagnosed clinically by physician as having Prediabetes. Criteria for the Diagnosis of Prediabetes and Diabetes (9) as shown in Table (1-1)

To have an idea about the normal values of study parameters and in order to assess how much the drug used in the study were able to normalize the abnormal parameters, other 20 in addition to 50 patients.

Patients : this study included, 25 patients treated with dietary control and life style modifications for 12 weeks, 25 patients treated with Q_{10} (200mg) plus dietary control and life style modifications for 12 weeks.

Table (1-1) Criteria for the Diagnosis of Prediabetes and Diabetes

	Prediabetes	Diabetes
A1C	5.7–6.4%	≥6.5%**
FPG	100–125 mg/dL (5.6-6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)**
OGTT*	140–199 mg/dL (7.8-11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)**
RPG		≥200 mg/dL (11.1 mmol/L)***

*2-hour plasma glucose value after a 75-g OGTT

**Confirm results with repeat testing.

***Diagnostic in patients with established symptoms of hyperglycemia

A1C, glycated hemoglobin; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test, RPG, random plasma glucose

Measurement of glycemic control : {A} Fasting blood sugar Level (FBS) , Serum glucose level was evaluated using a ready-made kit for this purpose, according to the method of (10) , which is based on enzymatic oxidation of glucose to form glucuronic acid and hydrogen peroxide, and the reaction of the later with phenol and formation of quinonimine was followed spectrophotometrically at 505 nm. Results were expressed as mg/dl, based on comparison with a standard glucose solution treated with same method . **{B} Glycated Hemoglobin (HbAlc)** , The Bio-Rad VARIANTTMhemoglobinAlC program is intended for the determination of HbA1c in human whole blood using the principles of ion exchange high performance liquid chromatography (HPLC) for the automatic and accurate separation of hemoglobinAlC (HbAlC). It is fully automated assay using HPLC technology to deliver precise and accurate HbA1c results. Program offer a simple preparation followed by automatic sampling, and an analysis time of three minutes per sample. Preceding analysis, a simple preparation of the sample is required to hemolyze and remove labile A1C. Samples are first diluted with hemolysis reagent and then incubated at 18-28Co for a minimum of 30 min. The VARIANTS II dual-piston pumps deliver a programmed buffer gradients of increasing ionic strength to the analytical cartridge. Prepared samples are automatically injected into analytical cartridge where the hemoglobin is separated based on their ionic interaction with the material. The separated hemoglobin then passes through the flow cell of the filter photometer, where changes in the absorbance at 415 nm are measured. A chromatogram of the changes in the absorbance is plotted versus the retention time. This chromatogram helps in result interpretation (11). **{C} Serum Insulin levels** , The Demeditec insulin ELISA is a solid phase ELISA based on sandwich principle. The microtiter wells are coated with a monoclonal antibody directed towards a unique antigenic site on the insulin molecule. An aliquot of patient sample containing endogenous insulin is incubated in the coated well with enzyme conjugate which is anti-insulin antibody conjugated with Biotin. After incubation the unbound conjugate is washed off. During the second incubation step Streptavidin –Peroxidase –Enzyme complex binds to the biotin-anti-insulin-antibody .the mount of (HRP) complex is proportional to the concentration of insulin in the sample. Having added the substrate solution, the intensity of the color developed is proportional to the concentration of Insulin in the patient sample. The result expressed as uU/ml. **{D} insulin resistance** , The HOMA model is simple and accessible measurement method for the evaluation of insulin sensitivity and consider as a model of interactions between glucose and insulin dynamics that is then used to predict fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and β-cell function. Both the original HOMA and the updated HOMA2 assume a feedback loop between the liver and β-cell (12, 13) glucose concentrations are regulated by insulin-dependent HGP, whereas insulin levels depend on the pancreatic Bcell response to glucose concentrations. Thus, deficient β-cell function reflects a diminished response of β-cell to glucose-stimulated insulin secretion. Likewise, insulin resistance is reflected by diminished suppressive effect of insulin on HGP. HOMA describes this glucose insulin homeostasis by a set of empirically derived nonlinear equations. The model predicts fasting steadystate levels of plasma glucose and insulin for any given combination of pancreatic β-cell function and insulin sensitivity (14). The approximating equation for IR has been simplified and uses a fasting plasma sample in which glucose (fasting plasma glucose; FPG) and insulin (fasting plasma insulin; FPI) are measured, together with a constant. The product of FPG×FPI is an index of IR .

$$\text{HOMA-IR} = (\text{glucose} \times \text{insulin})/405.$$

Insulin concentration is reported in uU/ml and glucose in mg/dl. The constant of 405 is a normalizing factor, i.e. normal FPI of 5 uU/mL × the normal FPG of 81 mg/dl typical of a 'normal' healthy individual = 405 . Therefore, for an individual with “normal” insulin sensitivity, HOMA-IR =1.

Statistical analysis : Paired Student’s t test was used to compare values obtained before and after treatment administration within each group while independent sample t tests were used for between all patients and healthy subjects. Multiple comparisons were also carried out by using Analysis of variance (ANOVA) with LSD post-hoc testing to compare changes in variables between groups before and after the 12 weeks treatment period. Data are presented as mean ± Standard deviation (SD). For all statistical analyses, $P<0.05$ was considered statistically significant using a two-tailed test. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 16.0 (15).

RESULTS

Comparison of patients with prediabetic and healthy subjects with respect to different parameters: In healthy group, the mean± SD for F.B.S, HbA1c, Fasting S.Insulin, Insulin resistance were 83.42±9.73, 5.12±0.064, 11.14±1.225 and 2.84 ±0.712 respectively.

In patients group the mean± SD for for F.B.S, HbA1c, Fasting S.Insulin, Insulin resistance were 119.42±5.555, 6.138±0.092, 13.54±1.888 and 3.994±0.604 respectively.Unpaired t-test was used to compare the baseline characters between the healthy and prediabetic patients group, revealed that were significant differences in F.B.S, HbA1c, Fasting S.Insulin and Insulinresistance ($p<0.001$) levels between both groups as shown in table (1-2).

Table (1-2) Comparison of different parameters of prediabetic patients to that of healthy subjects at baseline

Parameters	Patients		Healthy		P. value
	mean	±SD	mean	±SD	
F.B.S mg/dl	119.42	5.555	83.42	9.73	.001
HbA1C %	6.138	0.092	5.12	0.064	.001
Fasting Insulin	13.54	1.888	11.14	1.225	.001
In.resistance	3.994	0.604	2.84	0.712	.001

Effect of study treatment on (F.B.S , HbA1c , Fasting Insulin and Insulin resistance): study treatment demonstrated a significant decrease in the F.B.S, HbA1c, Fasting Insulin and Insulin resistance at the end of 12 weeks ($P<0.05$) compared with baseline measurements. In comparing with control group , the reductions in F.B.S , Fasting Insulin and in In.resistance was significantly at week 12 of the study ($P<0.05$), While the reduction in HbA1c was not significant.

Table (1-3) Effect of study treatment on **(Fasting blood sugar , HbA1c , Fasting Insulin and Insulin resistance)** after 12 week treatments in study group and multiple comparison of the change from baseline

Groups parameters		Control		Coenzyme Q10	
		mean	±SD	mean	±SD
F.B.S	Baseline	118.12	5.42	116.55	4.34
	12week	107.25*	4.97	98.21*	4.28
	ΔF.B.S	-10.87	1.22	-18.34[a]	1.12
HbA1c	Baseline	6.22	0.084	6.25	0.092
	12week	6.1*	0.081	6.01*	0.091
	ΔHbA1c	-0.09	0.022	-0.24	0.017
Fast.In	Baseline	12.44	1.17	12.27	1.22
	12week	11.09*	1.13	10.12*	1.07
	ΔFast.In	-1.35	0.14	-2.15[a]	0.17
In.resi	Baseline	3.61	0.34	3.53	0.35
	12week	2.94*	0.33	2.44*	0.38
	ΔIn.resi	-0.67	0.07	-1.09[a]	0.02

Fast.In:Fasting Insulin ,**In.resi**:Insulin resistance

*=statistically significant ($P<0.05$)difference after 12 weeks compared with the baseline by using paired t-test .

a= statistically significant ($P<0.05$)difference after 12 weeks compared with control group using ANOVA post hoc test or upaired t-test.

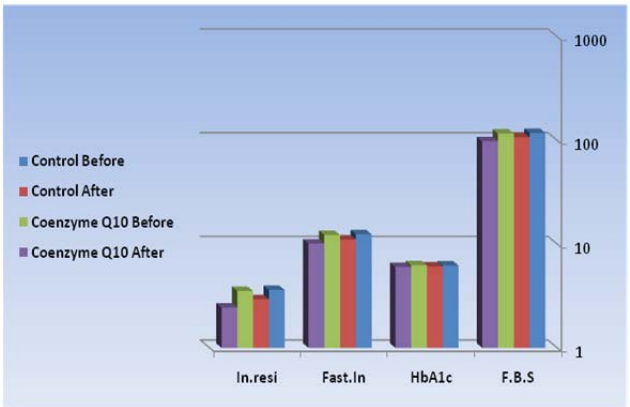

Figure (1-1) **F.B.S, HbA1c, Fast.In** and **In.resi** before and after 12 week of the study treatment

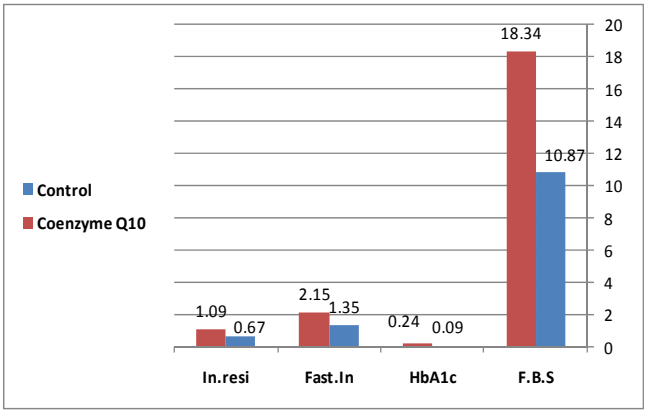

Figure (1-2) **Change in F.B.S, HbA1c, Fast.In** and **In.resi** after 12 week of the study treatment

DISCUSSION

Study treatment demonstrated a significant decrease in the F.B.S, HbA1c, Fasting Insulin and Insulin resistance at the end of 12 weeks ($P<0.05$) compared with baseline measurements. In comparing with control group , the reductions in F.B.S , Fasting Insulin and in Insulin resistance was significantly at week 12 of the study ($P<0.05$), While the reduction in HbA1c was not significant.

Lim et al., (2006) revealed profound changes in plasma CoQ10 in individuals with diabetes, suggesting a marked increase in body oxidative burden. Similar changes were already present in the prediabetic phase and may contribute to the increased risk of vascular diseases (16). Clinical monitoring of plasma CoQ10 concentration and its redox status is considered desirable as it may provide valuable pathophysiological or therapeutic information in vivo (17). The accumulating evidence has been suggested that mitochondrial dysfunction induced by oxidative stress plays a pivotal role in the pathogenesis of insulin resistance and vascular disease in subjects with diabetes (18). The BMI (a close surrogate of insulin resistance) and FPG were negatively correlated with the ubiquinol/CoQ10 fraction. This was not surprising, since insulin resistance and elevated blood glucose are associated with increased oxidative burden (19). The change in CoQ10 with increasing FPG concentration suggests an increase in oxidative burden, already evident in the prediabetic IFG individuals. This increase in oxidative stress might contribute to the increased risk of vascular disease (16). The reduction of glycation parameters and improve the insulin resistances in prediabetics patients is coincided with the mentioned studies that illustrated the role of CoQ10.

CONCLUSIONS:

According to the results presented in this study it is easy to conclude that the administration of Coenzyme-Q10 could improve glycemic control with consequent beneficial effects on oxidative stress in prediabetic patients, may be through mechanisms of up regulating peripheral tissue responses to the available insulin at receptor levels in association with potent antioxidant effects.

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