

# Role of L-carnitine and Coenzyme Q10 as Adjuvant Therapy in Patients with Type 2 Diabetes Mellitus

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**Abstract Objective:** To assess the effects of administration of L-carnitine and coenzyme Q10 on glycemic control, lipid profile and lipoprotein (a) when added to pre-existing oral antidiabetic drugs in patients with type 2 diabetes. **Methods:** Fifty seven type 2 diabetic patients were randomly assigned into three groups for treatment with L-carnitine (1g daily), coenzyme Q10 (150mg daily), or continued on the same oral antidiabetic drugs (sulfonylurea and metformin) and considered as control group. All patients have been kept on the same medications throughout the study. Patients followed up after 8 weeks of treatment. Fasting blood glucose, glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and lipoprotein (a) measured at baseline and after 8 weeks. **Results:** There is significant decrease in fasting blood glucose, total cholesterol, LDL-c and lipoprotein (a) in both L-carnitine group and coenzyme Q10 group after 8 weeks of treatment. In addition HbA1c% significantly decreased in coenzyme Q10 group compared to control group. There were no significant differences in HDL-c in all three groups. **Conclusion:** Supplementation with L-carnitine or coenzyme Q10 improve glycemic control in type 2 diabetic subjects when added to conventional antidiabetic medications and could help in reducing the risk of cardiovascular complications by reduction of LDL-cholesterol and lipoprotein (a).

**Keywords:** L-carnitine, Coenzyme Q10, type 2 diabetes, glycemic control, lipid profile, lipoprotein (a)

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## 1. Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Diabetes mellitus is a global chronic metabolic disorder that represent one of the most challenging health problems in the 21st century. People with diabetes have an increased risk of developing a number of serious health problems. Consistently high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys, nerves and teeth [2].

The prevalence of diabetes has been increasing steadily all over the world due to the rapid urbanization, nutrition transition, and increasingly sedentary lifestyles [3]. In 2013, 382 million people had diabetes; this number is expected to rise to 592 million by 2035. Most people with diabetes live in low- and middle-income countries [4]. Type 2 diabetes comprises 90% of people with diabetes around the world [1]. In type 2 diabetes mellitus there is a significant role of insulin resistance, oxidative stress, and dyslipidemia in pathogenesis of disease and its complication [5]. Chronic complications are the major

outcome of type 2 diabetes mellitus progress, which reduce the quality of life of patients, add heavy burdens to the health care system, and increase diabetic mortality [6]. Therefore there is a tremendous need for new management strategies which are safe and effective alone or in combination with existing drugs either for better control of the disease and/or prevent or delay its complications.

L-carnitine (l-3-hydroxy-4-N, N, N-tri-methylaminobutyrate) is a conditionally essential nutrient that plays a vital role in energy production and fatty acid metabolism. Carnitine is probably present in all animal species and in numerous micro-organisms and plants. In man L-carnitine synthesized from essential amino acid lysine [7]. L-carnitine has been recognized as a nutritional supplement in cardiovascular disease and there is increasing evidence that carnitine supplementation may be beneficial in treating obesity, improving glucose intolerance and total energy expenditure [8]. Food drug administration considered L-carnitine as a drug to treat the primary and secondary carnitine deficiency [9].

Coenzyme Q10 (2, 3-dimethoxy-5-methyl-6-decaprenyl benzoquinone) is fat-soluble vitamin-like quinone commonly known as ubiquinone [10]. Coenzyme Q10 (Q10) is vital for the proper transfer of electrons and adenosine triphosphate production within the mitochondrial

oxidative respiratory chain. Additionally, coenzyme Q10 has demonstrated activity in preventing lipid peroxidation and an indirect stabilizer of calcium channels to decrease calcium overload [11]. Coenzyme Q10 extensively studied as a critical adjuvant therapy for patients with cardiac diseases due to its beneficial effects on cellular bioenergetics, regulation of cell membrane channels and antioxidant effect [12]. However there is few studies with a conflicting results about its possible effects in type 2 diabetes patients.

It's well known that diabetes mellitus carries a high risk of cardiovascular complications, which remain the main cause of mortality in this population [13]. This study aimed to evaluate the proposed beneficial effects of short course (8 weeks) supplement of L-carnitine and coenzyme Q10 on glycemic control, total cholesterol, high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c) and lipoprotein (a) [Lp (a)] level which considered as a major risk factors for cardiovascular complications in patients with type 2 diabetes.

## 2. Subjects and Methods

### 2.1. Study Design

The present study was an 8-week randomized controlled single center clinical trial conducted at Specialized Center for Endocrinology and Diabetes, Al-Mawane General Hospital, Basra, Iraq carried out over 8 months from December 2013 till July 2014 at Specialized Center for Endocrinology and Diabetes, Al-Mawane General Hospital. Type 2 diabetes patients who treated with oral antidiabetic drugs (metformin and sulfonylurea) were randomly assigned into three groups to receive L-carnitine 1000 mg tablet once daily, Coenzyme Q10 75mg soft gel twice daily, or continued on the same oral antidiabetic drugs and considered as control group. L-carnitine was bought from Ultimate Nutrition Company, USA. Whereas Coenzyme Q10 was bought from Vitane's Nature Company, USA. Patients were evaluated at baseline and at week 8.

Informed consent was obtained from all participants and an ethical approval was obtained from Ethical Committee of College of Pharmacy / Baghdad University.

### 2.2. Sample Selection

Eligible patients were previously diagnosed with type 2 diabetes mellitus according to the American Diabetes Association (ADA) Criteria. All the patients should be on

the same oral antidiabetic drugs (sulfonylurea and metformin) for at least 3 consecutive months before the study and stabilized on same treatment throughout the study. Exclusion criteria include diabetic patients on insulin therapy, renal impairment, hepatic impairment, and patients with co-existent thyroid disorders, autoimmune or chronic inflammatory disease.

### 2.3. Laboratory Assessment

Blood sample was taken at baseline and after 8 weeks for analysis of FBG, HbA1c, TC, LDL-c, HDL-c, and Lp (a). Laboratory analysis was done by specialized laboratory researchers who did not participate in this study. FBG, TC, LDL-c and HDL-c analyzed by clinical chemistry analyzer (Biolyzer 300, Germany). Lp (a) was measured by latex-enhanced turbidimetric method using Lipoprotein (a) kit (Human, Germany). HbA1c measured by HbA1c-based D-10 Dual Program (Bio-Rad D-10, USA).

### 2.4. Statistical Analysis

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 19 for windows. Continuous variables were presented as mean  $\pm$  standard deviation (SD) and discrete variables were presented as numbers and frequencies. Chi square test for independence was used to test the significance of association between discrete variables. Continuous variables were checked by Q-Q plots and Shapiro Wilk test. ANOVA test was used to test the significance of difference in the mean of 3 independent samples in normally distributed continuous variables. The end values of each continuous variable were also compared with the baseline values of it by using paired sample *t*-test for normally distributed variables while Wilcoxon rank test for abnormally distributed variables. The findings with *P* values  $<0.05$  were considered significant.

## 3. Results

### 3.1. Patients

Of seventy five patients presented to the study only fifty seven patients (26 male and 31 female) were complete the study. Their age were  $51.07 \pm 7.27$  years (as mean  $\pm$  SD) and duration of diabetes was  $4.72 \pm 3.20$  years. There were no apparent differences between the three groups with respect to demographic data (Table 1).

Table 1. Patients characteristic at base line

Characteristics	l-carnitine group	CoQ10 group	Control group	p-value
Age in years	52.35 $\pm$ 6.97	49.37 $\pm$ 6.65	51.63 $\pm$ 8.13	NS
No. of patients	19	19	19	-----
Male: Female No. (%)	8:11 (41%)	10:9 (52%)	8:11 (42%)	NS
BMI*	29.47 $\pm$ 3.8	28.15 $\pm$ 4.08	29.5 $\pm$ 4.29	NS
Diabetes Duration( years)	5.53 $\pm$ 2.96	4.76 $\pm$ 3.98	3.97 $\pm$ 2.45	NS
Baseline HbA1c%	9.29 $\pm$ 2.15	8.23 $\pm$ 2.14	8.53 $\pm$ 1.94	NS

Data expressed as mean $\pm$ SD. \*BMI= body mass index, which is calculated according to the following formula: BMI= weight (kilogram)/height<sup>2</sup> (meter), NS= non-significant (*p* > 0.05).

### 3.2. Fasting Blood Glucose and Glycated Hemoglobin

Fasting blood glucose significantly ( $p < 0.05$ ) decrease in L-carnitine group compared to the baseline value, however no significant effect observed on HbA1c% after 8 weeks of treatment.

In Q10 group both FBG and HbA1c were significantly ( $p < 0.05$ ) decrease compare to control group (Table 2).

### 3.3. Lipid Profile and Lipoprotein (a)

Total cholesterol and LDL-c significantly decreased in both L-carnitine group and Q10 group compare to baseline value and non-significantly affected in control group. No significant effect on HDL-c was observed in all three groups.

Lipoprotein (a) were significantly ( $p < 0.05$ ) decrease in L-carnitine group and Q10 group after 8 weeks of treatment compared to baseline values and no statistical significant difference observed in control group (Table 2).

**Table 2. Changes from baseline and after 8 weeks in laboratory parameters for patients who completed the study**

Parameter	L-carnitine (19)	Coenzyme Q10 (19)	Control (19)
FBG(mg/dl)			
Before intervention	237.73±61.21	198.12±61.54	182.25±46.9
After intervention	196.4±77.62*	158.46±47.1*	191.89±49.57
% of change	-17.36%**	-20.02%**	5.28%
HbA1c (%)			
Before intervention	9.26 ± 2.06	8.4 ± 2.07	8.1 ± 1.61
After intervention	8.66 ± 1.87	7.3 ± 1.65*	8.5 ± 1.59
% of change	-6.54%	-13.08%**	5.01%
TC(mg/dl)			
Before intervention	203.06 ± 39.26	210.12 ± 75.84	187.39 ± 49.8
After intervention	184.5 ± 33.2*	180.9 ± 48.4*	198.82 ± 49.4
% of change	-9.14%	-13.89%	0.003%
LDL(mg/dl)			
Before intervention	110.15 ± 16.65	131.87 ± 42.05	100.33 ± 28.28
After intervention	101 ± 16.03*	108.92 ± 33.21*	115.11 ± 30.12
% of change	-8.3%	-15.57%	13.81%
HDL(mg/dl)			
Before intervention	41.78 ± 8.25	39.66 ± 6.74	41.56 ± 7.96
After intervention	42.24 ± 6.15	39.03 ± 7.49	37.7 ± 6.52
% of change	1.101%	-1.57%	-9.28%
Lp (a) (mg/dl)			
Before intervention	41.73 ± 18.13	39.92 ± 22.31	35.46 ± 26.84
After intervention	25.03 ± 9.47*	27.16 ± 7.27*	36.92 ± 25.55
% of change	-37.51%	-28.59%	3.85%

Data represented as mean±SD for baseline and end of study values;\* significantly different when compared to pre-treatment level within the same group ( $P < 0.05$ );\*\* significantly different when compared to control group ( $p < 0.05$ ).

## 4. Discussion

Diabetes mellitus is most common chronic disease worldwide. It's a growing cause of disability and premature death, mainly through cardiovascular disease [14]. Therefore it's requiring continuous medical care with multifactorial risk reduction strategies in addition to glycemic control to lower the risk of macro- and microvascular complications [15]. Carnitine covers important role in lipid and glucose metabolism as well as assisting in fuel sensing [16]. In addition Q10 play a key role in mitochondrial bioenergetics and plasma antioxidant effect and shown to improve lipid profile in serum, liver and muscle tissue in diabetic rat [17]. This work aims to evaluate the effect of L-carnitine (1g/day) or coenzyme Q10 (75mg bid) on some metabolic parameters in type 2 diabetes when added to oral antidiabetic drugs (metformin and sulfonylurea).

The present study shows that L-carnitine administration over the period of 8 weeks significantly reduce FBG without significant reduction in HbA1c% compared to control group. This result is in agreement with Hadadinezhad et al., who find significant reduction in FBS but no significant effect on HbA1c and 2-hour post prandial blood glucose and c-peptide level [18]. It's possible that improvement in glucose metabolism

insufficient to reach changes in glycated hemoglobin. However in Rahbaret al. study, L-carnitine shows a significant decrease in both FBG and HbA1c [19]. The lack of effect on HbA1c in this study may be attributed to short timeframe (8 weeks) of the study and lower dose of L-carnitine (1g/day) compared with Rahbar et al., who administer 3g/day of L-carnitine for 12 weeks. Abdelaleem et al. suggested that L-carnitine stimulates pyruvate dehydrogenase complex activity and enhances non-oxidative glucose metabolism by increasing in the mitochondrial acetyl carnitine efflux in the absence of exogenous fatty acids in isolated myocytes [20].

The study also showed that supplementation with coenzyme Q10 in a dose of 75 mg bid in combination with oral antidiabetic drugs associated with a significant decrease in both FBG and HbA1c after 8 weeks of intervention. This study is consistent with Hodgson et al., who report an improvement of long-term glycemic control after 12 weeks course of Q10 administration [21]. Several mechanisms suggested to explain the effect of coQ10 on glycemic control. Mezawa et al indicated that ubiquinol, the reduced form of Q10, improves insulin production and/or insulin secretion probably through activating mitochondrial ATP production in pancreatic beta-cells [22]. Moreover Q10 might reduce oxidative stress in mitochondria and this might improve insulin sensitivity and b-cell function [23]. The result of this study is inconsistent with Eriksson et al study, in which no

significant improvement in glycemic control observed in 23 type 2 diabetes who receive 200 mg/day Q10 or placebo for 6 months [24]. This inconsistency may attributed to small sample size in Eriksson et al and the differences in population, characteristics of patients and baseline HbA1c.

Both L-carnitine and Q10 show significant decrease in TC, LDL-c and Lp (a) after 8 weeks of treatment and non-significant effect on HDL-c.

Carnitine covers an important role in lipid metabolism, acting as an obligatory cofactor for beta-oxidation of fatty acids by facilitating the transport of long-chain fatty acids across the mitochondrial membrane as acylcarnitine esters [16]. Thus carnitine may shift the liver metabolism from esterification and synthesis of triglycerides toward the formation of acetylcarnitines. This could decrease synthesis of triglycerides and VLDL cholesterol [25]. Malaguarnera et al. observe a significant decrease in LDL cholesterol, oxidized LDL cholesterol, and triglycerides after 12 week in the carnitine-treated hypercholesterolemic newly diagnosed type 2 diabetes patients [26]. Effect of L-carnitine on lipids in this study is consistence with Alipuor et al in part that he also report decrease in TC and LDL in type 2 diabetic women with low caloric diet after 8 weeks of L-carnitine administration [27].

Conversely Rahbar et al [19] and González-Ortiz et al [28] show a non-significant effect of L-carnitine on TC and LDL-c in type 2 diabetic patients. This inconsistency in result could possibly attributed to relatively higher dose of L-carnitine (3 g/day) that used in Rahbar et al [19] and González-Ortiz et al [28] while in current work 1 g/day of L-carnitine used.

In addition Lp (a) shown to be reduced by significantly by administration of 1g/day of L-carnitine. This result confirm the result of Derosa et al [29] and Sirtori et al [30] who reported that 2 g/day of L-carnitine reduce plasma level of lipoprotein(a) in diabetic and non-diabetic patients respectively without clinically relevant adverse events.

Lipoprotein (a) appeared to be one of the most atherogenic lipoproteins and may be a potential risk factor for cardiovascular disease. It's composed of liver-derived apo(a) covalently bound to apoB, which is similar in lipid composition to apoB of LDL [31]. Lp(a) plasma level strictly under genetic control of and relatively refractory to both lifestyle and drug intervention [32]. Nicotinic acid derivative is the only lipid lowering drug that reduce Lp(a) levels by reduction in the circulating FFA inflow into hepatocyte [33], however its use limited by tolerability issues. L-carnitine plays an important role in the mitochondrial uptake of long-chain fatty acids by facilitating their transportation across the inner mitochondrial membrane to undergo  $\beta$ -oxidation and may reasonably reduce level fatty acid in flow for apo(a) production [34].

Coenzyme Q10 supplement leads to significant decrease in serum cholesterol, and LDL-c without significant effect on HDL-c. This result confirm the results of Mohammadi et al in which 64 type 2 diabetic patients receive either 200 mg Q10 or placebo daily for 12 weeks [35]. Q10 is a lipid-soluble substance that act as an intercellular antioxidant, and its presence was then demonstrated in all cell membranes and in blood, both in high- and in low-density lipoproteins [36]. Therefore reduction in lipid levels may be due to inhibition of LDL-

C oxidation. Chew et al shows that Q10 have no effect on lipid profile [37]. In chew et al study participants were typically overweight with satisfactory glycemic and lipid control while Q10 appears to be effective in hypercholesterolemic condition [38]. Q10 also significantly reduce Lp (a) but the magnitude of the effect variable among subjects, with some patients show a marked decrease and others only marginal change occur. Shojaei et al show that coenzyme Q10 in a dose of 100 mg/d is associated with a significant decrease in serum lipoprotein(a) level in maintenance hemodialysis patients [39]. Cicero et al demonstrated that adding CoQ10 to fenofibrate could improve the drug's efficacy in hypertriglyceremia patients not responding to fenofibrate alone [40]. Mechanisms by which Q10 can decrease serum Lp (a) not well known. Q10 was recognized to have an effect on gene expression [41]. Supplementation with coenzyme Q10 can inhibit expression of lipoprotein (a) receptor and result in decreased serum lipoprotein (a) [42].

## 5. Conclusion

Administration of L-carnitine (1g/day) and coenzyme Q10 (75mg bid) improve glycemic control, reduce total cholesterol and LDL-cholesterol in patient with type 2 diabetes when added to pre-existing oral antidiabetic drugs. L-carnitine and coenzyme Q10 also reduce lipoprotein (a) and thus may provide a protective effect against cardiovascular disease in diabetic patients. Further larger and longer studies are warranted to confirm these findings.

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