RESEARCH ARTICLE

Assessment of Some Clinical and Biochemical Parameters after Combining Coenzyme Q10 to Statin in Dyslipidemic Patients

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ABSTRACT

Background: Statins are the most popular treatment for the primary and secondary causes of cardiovascular diseases. Many controlled trials have demonstrated significant depletion of coenzyme Q10 (CoQ10) serum levels secondary to statin therapy.

Objectives: The current study was designed to investigate the effects of coenzyme Q10 (CoQ10) supplement in hypercholesterolemia patients receiving conventional atorvastatin treatment based on objective clinical and laboratory assessment.

Methods: This interventional prospective randomized controlled, open-label study, enrolled 52 dyslipidemic patients diagnosis with statin-associated muscle symptoms (SAMS) randomized into; Group 1: (n=20) received 200 mg/day of CoQ10 adjuvant to atorvastatin therapy. Group 2: (n=19) on atorvastatin only, both followed up for 12 weeks. Laboratory assessment of serum CoQ10 level, creatine phosphokinase (CPK), lipid peroxidation, SAMS, lipid profile, liver enzymes, and metabolic parameters was assessed.

Results: CoQ10 adjuvant therapy produced restoration and increased serum CoQ10 level (86.73%) compared to a notable decrease in mean serum CoQ10 end line level (-19.21%) in the control group on atorvastatin therapy alone. Also, CoQ10 adjuvant therapy produced a significant decrease in serum CPK, IL-6, MDA levels, TG, and a marked increase in serum HDL-C among intervention group patients only ($p \leq 0.01$), and they were negatively correlated with increased serum CoQ10 in those patients ($p \leq 0.01$).

Conclusions: CoQ10 adjuvant therapy benefits various clinical and biochemical outcomes in statin-associated muscular complaints dyslipidemic individuals.

Keywords: Clinical and biochemical markers, Coenzyme Q10, Statin-associated muscle symptoms dyslipidemia.

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INTRODUCTION

As a cardiovascular health concern, dyslipidemia affects more than one-third of adults in the United States.[1] Hypertension, sedentary lifestyle, obesity, diabetes mellitus, fatty/oily foods, excessive alcoholism and smoking, hypothyroidism, and metabolic syndrome are all risk factors for dyslipidemia. The initial step in treating dyslipidemia was to improve one's lifestyle, but this was difficult to achieve in the elderly; thus a combination of lifestyle adjustments and pharmacological therapy was used.[2] A healthy lifestyle can minimize the risk of ASCVD at any age, and it can even prevent the formation of risk factors in younger patients.[3]

Statins are important medications that lower cholesterol and lower the risk of cardiovascular disease.[4] Previous statin clinical trials have shown that lowering cholesterol by 20 mg/dL reduces the annual incidence rate of vascular events by 10–15%. However, there is significant inter-individual variance in the response of low-density lipoprotein cholesterol (LDL-C) to statins and may partially be determined on a genetic basis.[5] Because symptoms are subjective and there is no "gold standard" diagnostic test, a reliable diagnosis of SAMS is challenging. The (ACC/AHA/NHLBI) have established SAMS definitions based on symptoms and the amount of CPK elevation; nevertheless, clinical diagnostic criteria have received less attention.[6] Males have normal serum CPK levels of (50-200) IU/L, while females have normal serum CPK levels of (40-170) IU/L.[7] Many controlled trials have shown that statin

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medication causes considerable CoQ10 depletion (statins can lower CoQ10 serum levels by up to 40%).[8]

CoQ10 protects cellular membranes from free radical-induced oxidative stress (OS) by acting as a lipid-soluble antioxidant (both mitochondrial and extra-mitochondrial).[9] CoQ10 is involved in regenerating the antioxidants vitamin C and vitamin E and acting as an antioxidant directly.[10] Furthermore, data indicate that CoQ10 can act as an anti-inflammatory.[11]

The goal of this trial was to see if adding a CoQ10 supplement to the standard atorvastatin medication for hypercholesterolemia patients who had SAMS would help them feel better (statin-associated muscle symptoms). The current investigation is based on objective clinical and laboratory measurements of serum CoQ10, CPK, lipid peroxidation and inflammatory biomarkers, lipid profile, liver enzymes, and metabolic parameters.

PATIENTS AND METHODS

A total of 52 patients enrolled in this study, only (39) patients complete objective assessment for all study parameters. The research proposal was discussed and approved by the Scientific and Ethics Committee in the College of the Pharmacy, University of Mustansiriayah, and the agreement of Al-Yarmouk Teaching Hospital, Baghdad was achieved according to the Ministry of Health ethical committees.

Participants meet the inclusion criteria as;

- Those patients treated for dyslipidemia with a statin (at a dose and duration for the achievement of target levels of LDL-C) reported muscle symptoms; (pain, and (or) weakness, and (or) fatigue, and (or) cramps).
- Patients met the study definition for "myalgia",[12] as they reported new or increased muscle pain, cramps, or aching not associated with exercise, symptoms persisted for at least two weeks, symptoms resolved within two weeks of stopping the study drug, and symptoms reoccurred within 4 weeks of restarting the study medication.
- Patients on atorvastatin (20, 40) mg (their regimen had been previously adjusted due to muscular pain either by reduce, change the dose of statin withdrawal) within the last 3 months.
- Patients using statins for any comorbidity have a lipid profile altered [CAD, peripheral vascular disease, diabetes, or metabolic syndrome].

Definite exclusion criteria were attended to escape interference with the study design and include mainly Patients with other identified causes of myopathy or a history of myalgia before starting statin medication and those with a history of severe rhabdomyolysis (CPK > 10 UNL).

Study Design

The present study is an interventional prospective randomized controlled, open-label conducted from September 2019 to January 2021 and designed to investigate the effects of CoQ10 adjuvant therapy in dyslipidemia patients. The eligible patients were divided into two main groups: Intervention group 1 includes (28) patients with dyslipidemia treated with atorvastatin (20, 40) mg for (4–12 weeks), presented with SAMS, supplemented with 200 mg/day CoQ10, and followed up for 12 weeks. Control group 2 includes (24) patients with dyslipidemia treated with atorvastatin (20,40) mg for (4–12 weeks), presented with SAMS, without CoQ10 Supplementation and followed up for 12 weeks. Throughout the trial period, all patients continued to take open-label statins of the type and dose given by their physician; the statin dose and type remained unchanged.

METHODS

Measurement of serum coenzyme Q10 levels using an enzyme-linked immunosorbent assay (ELISA) kit (CSB-E14081h; Cusabio) with a detection range of 1.56 to 50 ng/mL[13] was part of the objective assessment of research parameters. The mean level in a healthy volunteer (49.43 ng/mL) was used as a reference.[14] CPK ELISA kit (MBS3801005) was used to measure serum creatinine phosphokinase (CPK), with a detection range of (0–200) U/L.[15] Interleukin-6 (IL-6) is a serum inflammatory marker that may be measured using a quantitative sandwich enzyme immunoassay approach (CSB-E04638h-cusabio), with a detection range of 0 to 500 pg/mL.[16] Malondialdehyde (MDA), a serum lipid peroxidation marker, was quantified using a double-sandwich ELISA method (MBS263626) kit with a detection range of 1.56–100 nmol/mL.[17] Based on an enzyme-driven reaction, the kits' assay was used to assess total cholesterol, triglyceride, high- and low-density lipoprotein-cholesterol levels in the serum, as determined by routine clinical chemistry laboratory assays (full automated dimension). Finally, fasting blood glucose (FBG) was assessed using an enzyme-driven reaction called enzymatic oxidation of glucose, liver enzymes Alanine and Aspartate aminotransferase (ALT, AST) were examined using a biochemical kit approach called antibody conjugate. Standard clinical chemistry laboratory testing determines these parameters (by using a fully automated -dimension device).

RESULTS

Patients Demographic and Disease Characteristics

The baseline characteristics of participants in study groups (52 patients) are presented in Table 1.

Baseline Values of Laboratory and Clinical Parameters

Table 2 showed no significant differences ($p > 0.05$) among means of laboratory and clinical parameters at baseline measurements between intervention group 1 and control group 2. The only significant differences showed for DBP (p-value ≤ 0.05).

Effect of the Study intervention on Laboratory and Clinical Parameters.

Table 3 showed a decrease in mean serum CoQ10 end line level (-19.21%), group 2 patients, and striking increases in mean serum CoQ10 end line level, for group one patients, about (86.73%) with a highly significant difference noted between study groups following 12 weeks of intervention ($p \leq 0.01$).

Table 1: Patients demographic data and disease characteristics at baseline

Variables		*Group 1*		*Group 2*		
N		*N*	*Percent (%)*	*N*	*Percent (%)*	*p-value*
Sample size		28	54	24	46	0.431N.S
Gender	Male	14	50	13	54	0.764N.S
	Female	14	50	11	46	
Age (years)		59.24 ± 5.571		58.11 ± 7.10		0.523N.S
BMI (kg/m^2)		32.54 ± 4.66		31.59 ± 5.08		0.311N.S
Blood pressure	SBP, mmHg	13.32 ± 0.67		13.08 ± 1.79		0.543N.S
	DBP, mmHg	9.07 ± 1.08		8.13 ± 0.95		0.001**
Duration on statin therapy (weeks)		7.29 ± 2.83		7.17 ± 2.70		0.878N.S
History of statin therapy (months)		16.678 ± 11.76		16.791 ± 13.75		0.975N.S
Medical history	DM, patients	10	36	10	42	0.66N.S
	HT, patients	20	71	20	83	0.298N.S
	IHD, patients	10	36	9	38	0.894N.S
Atorvastatin dose	20 mg	23	82	18	75	0.532N.S
	40 mg	5	18	6	25	
Number of current drugs	≤ 4 drugs	21	75	14	58	0.199N.S
	> 4 drugs	7	25	10	42	

Data presented as mean ± SD, Number of patients (N), Percentage (%), Independent *t*-test is used for statistical analysis of (age, BMI, duration, blood pressures, history of statin therapy), Chi-square is used for statistical analysis of numerical parameters in (gender), while Fisher t-test is used for statistical analysis of (medical history, atorvastatin dose, and the number of drugs).
N.S: No significant differences (*P*-value > 0.05), ** (P-value ≤ 0.01) is considered highly significant SD= standard deviation, BMI=body mass index, SBP= systolic blood pressure, DBP=diastolic blood pressure, DM= Diabetic multiuse, HT= hype rtension, IHD=ischemic heart disease."

Table 2: Baseline values of laboratory and clinical parameters.

	Group 1 (N=20)			*Group 2 (N=19)*			
Variable	*Mean*	±	*SD*	*Mean*	±	*SD*	*p-value*©
CoQ10, ng/mL	21.22	±	4.50	21.91	±	6.33	0.697 N.S
CPK, U/L	117.52	±	21.71	118.60	±	21.51	0.877 N.S
IL6, pg/mL	5.00	±	3.48	4.77	±	4.91	0.865 N.S
MDA, nmol/mL	15.69	±	4.47	13.44	±	3.02	0.075 N.S
ALT, U/L	27.10	±	8.84	25.00	±	8.24	0.448 N.S
AST, U/L	21.25	±	6.55	22.42	±	6.38	0.575 N.S
HDL-C mg/dL	34.66	±	7.06	35.37	±	4.47	0.710 N.S
TG, mg/dL	168.60	±	39.52	176.95	±	51.58	0.573 N.S
TC mg/dL	189.90	±	25.26	188.32	±	32.41	0.865 N.S
LDL-C mg/dL	121.53	±	24.27	117.56	±	31.20	0.659 N.S
FBG, mg/dL	147.35	±	55.68	152.11	±	65.34	0.808 N.S
SBP, mmHg	133.5	±	6.7	130.0	±	17.6	0.413 N.S
DBP, mmHg	89.3	±	10	82.1	±	9.8	0.030*
BMI, kg/m2	32.59	±	4.59	30.52	±	4.99	0.184 N.S

©: Independent t-test were used, N.S: non-significant (p > 0.05), * significant (p < 0.05). CoQ10= Coenzyme Q10, CPK=Creatinine phosphokinase, IL6=Interleukin-6, MDA= Malondialdehyde, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, HDL-C=high-density lipoprotein, TG=triglyceride, TC=total cholesterol, LDL-C= low-density lipoprotein cholesterol, FBG=fasting blood glucose, SBP= systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index. "

Serum CPK mean level was strikingly reduced in CoQ10 supplemented group about (-10.66%), while no marked increase in control/group 2 patients with a statistically high significant difference (p≤ 0.01) between groups at end line time. Also, there was a highly significant difference (p≤0.01) between study groups 1 and 2, in the mean end line time

of serum (IL-6), and (MDA) presented with an increase by (6.10%) for group two patients, while a decrease in an oxidative marker by (-33.84%) for group 1 patients. A decreased mean serum ALT by (-14.30 %, and -10.01 %) for group 1 and group 2, respectively, while serum AST means decreased by (-7.42 % in group 1), but no reduction (in group 2) were recognized and no-significant changes showed in liver enzymes ($p > 0.05$) between study groups after 12 weeks. A significant difference ($p \leq 0.05$) was noted in HDL-C (elevated in both study groups with marked elevation noticed 21% for group 1 and 12.49 % for group 2). And highly significant difference ($p \leq 0.01$) was observed between patients in the study groups after 12 weeks of follow-up, in TG (decreased in group1 patients -24.65% while a slight increase was noted in group 2 about 9.58%). At the same time, no significant difference was observed in LDL-C between the study group patients and TC (decreased for both groups, but higher percent recognized for group 1). FBG decreased at the end line time of the study regarding metabolic parameters by (-15.28% and -8.80%). While a highly significant difference ($p \leq 0.01$) in DBP end line means (higher percent decrease in group 1 patients -11.42% in comparison to only -0.93% for group 2), SBP end line means presented with no significant difference (but decreased by -6.07% for group 1 with a slightly increased by 0.46 % for group two patients). BMI presented with no significant difference ($p > 0.05$) between study groups.

Correlation of Serum Coenzyme Q10 Endline Level with Laboratory and Clinical Parameter.

Results in the table (4) revealed that correlations of serum CoQ10 level at end line for group 1 (interventional) was a positive highly significant ($p \leq 0.01$) with HDL, and highly negative considerable correlation with TG, MDA, and IL6. In contrast, serum CoQ10 end line level for group 2 (control) showed no significant correlations ($p > 0.05$) with laboratory

Table 3: Effect of the study intervention on laboratory and clinical parameters.

Variable	*Study group*	*Estimated baseline*	*End line*		*P-value*©	*% of difference*
			Mean	*± SD*		
CoQ10, ng/mL	Group 1	21.55	40.24	6.35	0.001**	86.73
	Group 2		17.41	5.21		-19.21
CPK, U/L	Group 1	118.05	105.47	18.87	0.002**	-10.66
	Group 2		122.32	19.03		3.62
IL-6, pg/mL	Group 1	4.88	3.63	1.86	0.003**	-25.61
	Group 2		6.26	4.09		28.28
MDA, nmol/mL	Group 1	14.60	9.66	4.30	0.001**	-33.84
	Group 2		15.49	4.21		6.10
ALT, U/L	Group 1	26.08	22.35	6.69	0.26 N.S	-14.30
	Group 2		23.47	9.83		-10.01
AST, U/L	Group 1	21.82	20.20	5.76	0.307 N.S	-7.42
	Group 2		22.16	5.06		1.56
HDL-C, mg/dL	Group 1	35.00	42.35	7.27	0.044*	21.00
	Group 2		39.37	5.59		12.49
TG, mg/dL	Group 1	172.67	130.10	33.44	0.001**	-24.65
	Group 2		189.21	68.31		9.58
TC, mg/dL	Group 1	189.13	148.25	37.65	0.059	-21.61
	Group 2		168.84	33.16		-10.73
LDL-C, mg/dL	Group 1	119.59	79.88	37.10	0.247 N.S	-33.21
	Group 2		91.63	38.47		-23.38
FBG, mg/dL	Group 1	149.67	126.8	49.28	0.456 N.S	-15.28
	Group 2		136.5	57.81		-8.80
SBP, mmHg	Group 1	131.8	123.8	19.5	0.095 N.S	-6.07
	Group 2		132.4	14.6		0.46
DBP, mmHg	Group1	85.8	76.0	10.9	0.001**	-11.42
	Group 2		85.0	8.7		-0.93
BMI, kg/m^2	Group 1	31.58	31.52	4.44	0.056 N.S	-0.19
	Group 2		31.24	3.80		-1.08

Data presented as mean ± SE, © Analysis of covariance were used, N.S: non-significant ($p > 0.05$), * ($p \leq 0.05$) is considered significant differences, ** ($p \leq 0.01$) is considered highly significant differences. CoQ10=Coenzyme Q10, CPK=Creatinine phosphokinase, IL6=Interleukin-6, MDA= Malondialdehyde, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, HDL-C=high-density lipoprotein, TG=triglyceride, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, FBG=fasting blood glucose, SBP= systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index. "

and clinical parameters following 12-weeks of intervention (end line).

DISCUSSION

Both 20, and 40 mg of high-intensity statins reduced serum CoQ10 by -19.21 in control participants after three months in the current investigation. Although several theories have been proposed, the mechanics remain unknown. To begin with, statin medication inhibited Farnesyl pyrophosphate, a precursor in the production of CoQ10, which could lead to a decrease in circulating/intramuscular CoQ10 levels.[18] Second, statin therapy may reduce dietary CoQ10 absorption.[19] Furthermore, aging can increase CoQ10 demand, contributing to low CoQ10 levels.[20] Moreover, after supplementation with 200 mg/day of CoQ10 for three months, the current findings showed a significant increase in serum CoQ10 concentration ($p \leq 0.01$), compared to a group with conventional atorvastatin treatment. Keith *et al* reported that Supplementation could help patients taking statins raise their plasma levels of CoQ10.[21] A Previous study showed that CoQ10 supplementation (30–300 mg/day) in statin-treated patients reversed statin-induced declines in total CoQ10 levels and produced 25–300% increases in serum CoQ10 levels.[22]

Creatine kinase level was decreased by (-10.66%) after CoQ10 adjuvant treatment as presented in the current study. CoQ10 treatment did not reduce plasma CPK in previous clinical investigations and a meta-analysis, independent of the provided dosage of CoQ10 or the duration of CoQ10 Supplementation, as compared to placebo.[23] In this study, both group patients presented without physical activity since large increases in CPK levels have been observed in runners on statins, and the strength of this link has been stronger with age;[24] this may explain why patients CPK level presented within limits of normal in both study groups (117.52 ± 21.71 and, 118.60 ± 21.51 U/L) respectively. The CPK level was negatively correlated though non-significant (*p*-value =0.18, r= -0.31) with the increase in serum CoQ10 level at the end of the study. Inversely, CoQ10 supplementation reduced exercise-induced muscle damage as determined by the CPK level in a study of Japanese male athletes.[25]

Table 4: Correlation of serum CoQ10 level end line with laboratory and clinical parameters.

	Serum Coenzyme Q10-end line			
	Group 1		*Group 2*	
Parameters	*R*	*P-value*	*R*	*P-value*
CPK, U/L	-0.31	0.18 $^{N.S}$	0.41	0.09 $^{N.S}$
IL6, pg/mL	-0.58	0.01**	-0.2	0.41 $^{N.S}$
MDA, nmol/mL	-0.78	0.001**	-0.26	0.28 $^{N.S}$
ALT, U/L	0.36	0.12 $^{N.S}$	0.05	0.84 $^{N.S}$
AST, U/L	-0.2	0.4 $^{N.S}$	0.31	0.19 $^{N.S}$
HDL-C, mg/dL	0.78	0.001**	0.03	0.9 $^{N.S}$
TG, mg/dL	-0.55	0.01**	-0.35	0.15 $^{N.S}$
TC, mg/dL	0.19	0.42 $^{N.S}$	-0.42	0.07 $^{N.S}$
LDL-C, mg/dL	0.14	0.56 $^{N.S}$	-0.24	0.31 $^{N.S}$
FBG, mg/dL	0.13	0.57 $^{N.S}$	0.08	0.74 $^{N.S}$
SBP, mmHg	-0.16	0.51 $^{N.S}$	-0.3	0.21 $^{N.S}$
DBP, mmHg	-0.22	0.35 $^{N.S}$	-0.04	0.86 $^{N.S}$
BMI, kg/m^2	-0.3	0.2 $^{N.S}$	-0.15	0.53 $^{N.S}$

"Bivariate Pearson correlations, N.S: non-significant ($p > 0.05$), **Correlation is highly significant at the 0.01 level (2 tailed)."
CPK=Creatinine phosphokinase, IL-6=Interleukin-6, MDA= Malondialdehyde, ALT= Alanine aminotransferase, AST=aspartate aminotransferase, HDL-C=high density lipoprotein, TG= triglyceride, TC= total cholesterol, LDL-C= low density lipoprotein cholesterol, FBG= fasting blood glucose, SBP= systolic blood pressure, DBP= diastolic blood pressure, BMI= body mass index.

Interleukin-6, rather than C-reactive protein (CRP), was a better predictor of cardiovascular disease. Atherosclerosis, peripheral vascular disease, coronary artery disease, type 2 diabetes, and obesity are all caused by interleukin 6-mediated inflammation, which is the gatekeeper and common causal factor for aging and age-related illnesses.[26] Recent data suggest that CoQ10, as an anti-inflammatory drug, can help with the inflammatory process in a variety of human disorders.[20] In 2016, CoQ10 supplementation reduced inflammatory marker (IL-6) in atherosclerotic individuals in a randomized, double-blind trial involving statin-treated individuals with dyslipidemia, compared to control.[27] In the current study, there was a (-25.61%) decrease in serum IL-6 level end line time in group 1 patients. This decrease was significantly correlated with an increase in serum CoQ10 level ($p \leq 0.01$, r = -0.58). This finding supports the additional anti-inflammatory effect obtained due to the CoQ10 supplementation, which applies to the previous study's finding.[28] But the difference presented for the control group results, in the current study group 2 patients on atorvastatin monotherapy showed an increase by (28.28%) in serum IL-6 end line level despite the anti-inflammatory effect of atorvastatin therapy. This is explained by the fact that IL-6 levels increased in response to standardized pain-inducing methods, indicating that inflammation increased.[29]

Coenzyme Q10 has anti-atherogenic properties and can reduce vascular inflammatory responses by preventing the oxidation of LDL particles (MDA), which is the most researched and important product of polyunsaturated fatty acid peroxidation.[30] Frankel and Neff (1983), argued that as a breakdown product, oxidized lipids were able to generate MDA.[31] MDA plasma levels were shown to be high in patients with non-insulin-dependent diabetic Mellitus (NIDDM),[32] heart disease patients with cardiovascular problems,[33,34] and atherosclerotic patients.[35] These comorbidities were the characteristics of the most enrolled participants of the current study, which explained the cause of elevation in the estimated baseline MDA serum level (14.6 mmol/L) when compared to the range (0–3) nmol/L obtained in healthy subjects.[36] In agreement with previous studies,[37,38] the current study found that MDA levels lowered by (-33.84 %) ($p \leq 0.01$) after week 12, and the decrease in MDA level was negatively correlated with the increased serum CoQ10 level ($p \leq 0.01$, r = -0.78).

In clinical trials, elevated liver transaminases (ALT and AST) have been found in roughly 2% of patients.[39] Several investigations have suggested that the increase in transaminases is minimal.[40] Plasma ALT and AST levels were not significantly different between the CoQ10 supplemented group and the atorvastatin-only treated group in a previous randomized study.[41] Although non-significant findings in the current study ($p > 0.05$), both measured liver enzymes were decreased in CoQ10 supplemented patients after 12 weeks by (-14.30%, and -7.42% for ALT and AST respectively), though no-correlation with serum CoQ10 level was observed. Even though the current study's findings in liver enzyme testing were non-significant, the percent of drop shown after CoQ10 administration was shown to have hepatoprotective benefits in statin-treated patients earlier. Using an in-vitro model, researchers discovered a link between hepatopathy and low CoQ10 levels caused by statin use.[42]

Dyslipidemia raises the risk of cardiovascular events by 2–6 times and all-cause mortality by 1.5 times in those with metabolic syndrome.[43,44] In the current study, CoQ10 adjuvant therapy had a significant impact on triglyceride and HDL levels in particular compared to the effect of atorvastatin monotherapy. After 12 weeks, an increase in serum HDL-C (21% and 12%) ($p \leq 0.01$) was observed in group 1, and group 2 patients, respectively. Moreover, a significant reduction of TG level was observed in the CoQ10 group at the end line (-24.65%) ($p \leq 0.01$). These changes in lipid profile were significantly correlated with serum CoQ10 level at the end of the current study. The effect of CoQ10 adjuvant therapy on serum TC and LDL-C results in a reduction by (-21.61% and -33.21%) were noticed respectively though non-significant. In addition, a meta-analysis of seven studies with CoQ10 adjuvant therapy found no positive benefits on lipid profiles in diabetic individuals[45] or obese people.[46] Nonetheless, CoQ10 could lower total cholesterol (TC) and LDL-C in non-statin-treated individuals but not in statin-treated patients.[47,48] Increased plasma TG levels (even when accompanied by reached target LDL-C) have now been demonstrated to enhance cardiovascular risk and induce atherogenesis.[49] And, in line with current findings, Zahedi *et al.,* (2014) CoQ10 treatment of 200 mg for 12 weeks reduced triglyceride levels.Increased serum HDL-C levels aid.[50] The reverse cholesterol transport mechanism.[51] In comparison to the results of a double-blinded randomized clinical trial in 52 Iranian patients with hyperlipidemia, the intake of CoQ10 (200 mg/day) for 12 weeks resulted in a significant increase in serum HDL-C and no statistical difference between the two groups in LDL-C, TC, and TG serum levels after the intervention.[52]

In the current study, there was a considered decrease in FBG (-15.28%) among patients in group1 after 12 weeks. Gholami *et al.* (2017) reported that 100 mg/day CoQ10 supplementation for 12 weeks for women with diabetes mellitus 2, resulted in lower fasting blood glucose levels and other metabolic indicators.[53] Zahedi *et al.* (2014) found a similar result.[50] Inversely, in type 2 diabetes patients supplemented with CoQ10 for 6 months, Eriksson *et al.* (1999)[54] showed no improvement in glycemic control or lipid levels, but it did not interfere with glycemic control. However, in previous randomized clinical trials conducted in healthy obese individuals,[46] or in a meta-analysis including six clinical trials in which CoQ10 was supplemented for12 weeks or less,[55] all failed to find a significant effect CoQ10 on glucose profile. This was close to the current finding, probably that 12 weeks of intervention of CoQ10 might not be enough. In the 24th week, CoQ10 consumption led to a significant decrease in FBG compared to placebo showed in a previous study.[55]

Two prior studies found that taking a CoQ10 supplement was well tolerated and did not cause any clinically significant changes in blood pressure.[56] On the other hand, Supplementation is not effective for individuals with decompensated hypertension; 100 mg of CoQ10 per day for 12 weeks did not result in any clinically significant changes in blood pressure.56 The present study showed that supplementation of CoQ10 for 12 weeks reduced SBP and DBP by an average of (-6.07% and -11.42%), respectively, and a significant effect was noticed in DBP only compared to patients on atorvastatin alone. However, the extent of change in blood pressure in current study patients was less than that seen in previous clinical studies in hypertensive patients,[57] possibly because the patients recruited had near-normal baseline blood pressure readings than hypertensive patients in previous studies. In the current study, the effects of CoQ10 adjuvant therapy showed no significant change in patients' BMI. However, no correlation with serum level of CoQ10 was seen. This could be due to the confusing influence of many simultaneous anti-diabetic, anti-hypertensive, and other therapies on the patients' weight. The non-significant change in BMI is consistent with the findings of a previous study.[54]

CONCLUSION

This study showed that CoQ10 adjuvant treatment has a favorable effect in dyslipidemic patients with statin-associated muscle complaints and that restoring serum CoQ10 levels after three months resulted in improvements in disease-related clinical and laboratory biomarkers.

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REFERENCES

1. Di Stasi SL, MacLeod TD, Winters JD, Binder-Macleod SA. Effects of statins on skeletal muscle: a perspective for physical therapists. Physical therapy. 2010 Oct 1;90(10):1530-1542.
2. Ali I, Kharma A, Samara M, Odeh S, Jaradat N, Zaid AN, Ahmad MA. Prevalence of Dyslipidemia in Undiagnosed Palestinian Men: A Cross-Sectional Study. Journal of lipids. 2018;2019.
3. Bitzur R, Cohen H, Kamari Y, Harats D. Intolerance to statins: mechanisms and management. Diabetes care. 2013 Aug 1;36(Supplement 2);S325-S330.
4. Chasman DI, Giulianini F, MacFadyen J, Barratt BJ, Nyberg F, Ridker PM. Genetic determinants of statin-induced low-

density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Circulation: Cardiovascular Genetics. 2012 Apr;5(2):257-264.
5. Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Journal of the American College of Cardiology. 2002 Aug 7;40(3):567-572.
6. Kajinami K, Tsukamoto K, Koba S, Inoue I, Yamakawa M, Suzuki S. Statin Intolerance Clinical Guide Working Group. (2019). Statin intolerance clinical guide 2018. Journal of atherosclerosis and thrombosis, 50948.
7. Hargreaves IP, Duncan AJ, Heales SJ, Land JM. The Effect of HMG-CoA Reductase Inhibitors on Coenzyme Q 10. Drug safety. 2005 Aug;28(8):659-676.
8. Hargreaves IP. Ubiquinone: cholesterol's reclusive cousin. Annals of clinical biochemistry. 2003 May 1;40(3):207-218.
9. Hargreaves I, Heaton RA, Mantle D. Disorders of human coenzyme q10 metabolism: An overview. International Journal of Molecular Sciences. 2020 Jan;21(18):6695.
10. Alam MA, Rahman MM. Mitochondrial dysfunction in obesity: potential benefit and mechanism of Co-enzyme Q10 supplementation in metabolic syndrome. Journal of Diabetes & Metabolic Disorders. 2014 Dec;13(1):1-11.
11. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, Chipkin S, Pescatello LS, Simpson K, White CM, Thompson PD. Effect of statins on skeletal muscle function. Circulation. 2013 Jan 1;127(1):96-103.
12. Human coenzyme Q10 (CoQ10) ELISA Kit (Catalog Number. CSB-E14081h) [product insert on the internet]. China: Cusabio.
13. Gurha N, Rehan HS, Yadav M, Gupta LK. Association of statin induced reduction in serum coenzyme Q10 level and conduction deficits in motor and sensory nerves: An observational cross-sectional study. Clinical Neurology and Neurosurgery. 2020 Sep 1;196:106046.
14. Human Creatine phosphokinase (CPK) ELISA Kit (Catalog Number. MBS3801005) [product insert on the internet]. USA: Biosource.
15. Human Interleukin 6 (IL-6) ELISA Kit (Catalog Number. CSB-E04638h) [product insert on the internet]. China: Cusabio.
16. Human Malondialdehyde (MDA) ELISA Kit (Catalog Number. MBS263626) [product insert on the internet]. USA: Biosource.
17. Wang LW, Jabbour A, Hayward CS, Furlong TJ, Girgis L, Macdonald PS, Keogh AM. Potential role of coenzyme Q 10 in facilitating recovery from statin-induced rhabdomyolysis. Internal medicine journal. 2015 Apr;45(4):451-453.
18. Caparrós-Martín JA, Lareu RR, Ramsay JP, Peplies J, Reen FJ, Headlam HA, et al. Statin therapy causes gut dysbiosis in mice through a PXR-dependent mechanism. Microbiome. 2017 Dec;5(1):1-5.
19. Vafa M, Can coenzyme Q10 supplementation effectively reduce human tumor necrosis factor- and interleukin-6 levels in chronic inflammatory diseases? A systematic review and meta-analysis of randomized controlled trials, Pharmacological Research (2019).
20. etabolism and Cardiovascular Diseases, 18(2), pp.105-111.
21. Keith M, Mazer CD, Mikhail P, Jeejeebhoy F, Briet F, Errett L. Coenzyme Q10 in patients undergoing CABG: Effect of statins and nutritional supplementation. Nutrition, Metabolism and Cardiovascular Diseases. 2008 Feb 1;18(2):
22. Mabuchi H, Nohara A, Kobayashi J, Kawashiri MA, Katsuda S, Inazu A, Koizumi J, Hokuriku Lipid Research Group. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis. 2007 Dec 1;195(2):e182-e189.
23. Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi DZ. Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. Journal of the American Heart Association. 2018 Oct 2;7(19):e009835.
24. Parker, BA, Augeri AL, Capizzi JA, Ballard KD, Troyanos C, Baggish AL. Thompson PD. Effect of statins on creatine kinase levels before and after a marathon run. The American journal of cardiology, 2012;109(2):282-287.
25. Kon M, Tanabe K, Akimoto T, Kimura F, Tanimura Y, Shimizu K, Okamoto T, Kono I. Reducing exercise-induced muscular injury in kendo athletes with supplementation of coenzyme Q10. British journal of nutrition. 2008 Oct;100(4):903-909.
26. Omoigui S. The Interleukin-6 inflammation pathway from cholesterol to aging–Role of statins, bisphosphonates and plant polyphenols in aging and age-related diseases. Immunity & Ageing. 2007 Dec;4(1):1-22.
27. Spišáková K, Pella J, Pella D. Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia. Journal of basic and clinical physiology and pharmacology. 2017 Jul 1;28(4):327-336.
28. Schaars CF, & Stalenhoef, AF. Effects of ubiquinone (coenzyme Q10) on myopathy in statin users. Current opinion in lipidology, 2008;19(6):553-557.
29. Lazaridou A, Martel MO, Cahalan CM, Cornelius MC, Franceschelli O, Campbell CM, Haythornthwaite JA, Smith M, Riley J, Edwards RR. The impact of anxiety and catastrophizing on interleukin-6 responses to acute painful stress. Journal of Pain Research. 2018;11:637.
30. Del Rio, D., Stewart, A. J., & Pellegrini, N. (2005). A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutrition, metabolism and cardiovascular diseases, 15(4):316-328.
31. Frankel EN, Neff WE. Formation of malonaldehyde from lipid oxidation products. Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism. 1983 Dec 20;754(3):264-270.
32. Dierckx, N., Horvath, G., Van Gils, C., Vertommen, J., Van de Vliet, J., De Leeuw, I., & Manuel-y-Keenoy, B. (2003). Oxidative stress status in patients with diabetes mellitus: relationship to diet. European journal of clinical nutrition, 57(8):999-1008.
33. Boaz M, Matas Z, Biro A, Katzir ZE, Green M, Fainaru M, Smetana S. Serum malondialdehyde and prevalent cardiovascular disease in hemodialysis. Kidney international. 1999 Sep 1;56(3):1078-1083.
34. Boaz M, Matas Z, Biro A, Katzir ZE, Green M, Fainaru M, Smetana S. Comparison of hemostatic factors and serum malondialdehyde as predictive factors for cardiovascular disease in hemodialysis patients. American journal of kidney diseases. 1999 Sep 1;34(3):438-444.
35. Tamer L, Sucu N, Polat G, Ercan B, Aytacoglu B, Yücebilgiç G, Ünlü A, Dikmengil M, Atik U. Decreased serum total antioxidant status and erythrocyte-reduced glutathione levels are associated with increased serum malondialdehyde in atherosclerotic patients. Archives of medical research. 2002 May 1;33(3):257-260.

Banjare J, Salunke M, Indapurkar K, Ghate U, & Bhalerao S. Estimation of serum malondialdehyde as a marker of lipid peroxidation in medical students undergoing examination-induced

psychological stress. Journal of the Scientific Society, 2017;44(3):137.
36. Mabuchi H, Nohara A, Kobayashi J, Kawashiri MA, Katsuda S, Inazu A, Koizumi J, Hokuriku Lipid Research Group. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis. 2007 Dec 1;195(2):e182-189.
37. Lee BJ, Huang YC, Chen SJ, Lin PT. Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with coronary artery disease. Nutrition. 2012 Mar 1;28(3):250-255.
38. Pek SL, Tavintharan S, Woon K, Lin L, Ong CN, Lim SC, Sum CF. MicroRNAs as biomarkers of hepatotoxicity in a randomized placebo-controlled study of simvastatin and ubiquinol supplementation. Experimental Biology and Medicine. 2016 Feb;241(3):317-30.
39. Russo MW, Scobey M, Bonkovsky HL. Drug-induced liver injury associated with statins. InSeminars in liver disease © Thieme Medical Publishers. 2009; Nov 29(4):412-422.
40. Mabuchi H, Nohara A, Kobayashi J, Kawashiri MA, Katsuda S, Inazu A, Koizumi J, Hokuriku Lipid Research Group. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis. 2007 Dec 1;195(2):e182-e189.
41. Tavintharan S, Ong CN, Jeyaseelan K, Sivakumar M, Lim SC, Sum CF. Reduced mitochondrial coenzyme Q10 levels in HepG2 cells treated with high-dose simvastatin: a possible role in statin-induced hepatotoxicity?. Toxicology and applied pharmacology. 2007 Sep 1;223(2):173-9.
42. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC medicine, 2011;9(1):1-13.
43. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes care, 2005;28(7):1769-1778.
44. Suksomboon, N., Poolsup, N., & Juanak, N. Effects of coenzyme Q10 Supplementation on metabolic profile in diabetes: a systematic review and meta-analysis. Journal of Clinical Pharmacy and Therapeutics, 2015;40(4):413-418.
45. Lee YJ, Cho WJ, Kim JK, Lee DC. Effects of coenzyme Q10 on arterial stiffness, metabolic parameters, and fatigue in obese subjects: a double-blind randomized controlled study. Journal of medicinal food, 2011:14(4):386-390.
46. Mabuchi H, Nohara A, Kobayashi J, Kawashiri MA, Katsuda S, Inazu A.,...Hokuriku Lipid Research Group. Effects of CoQ10 Supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis, 2007:195(2):e182-e189.
47. Samimi M, Zarezade Mehrizi M, Foroozanfard F, Akbari H, Jamilian M, Ahmadi S, Asemi Z. The effects of coenzyme Q10 supplementation on glucose metabolism and lipid profiles in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clinical endocrinology. 2017 Apr;86(4):560-566.
48. Newman, JW, Pedersen TL, Brandenburg VR, Harris WS, Shearer GC. Effect of omega-3 fatty acid ethyl esters on the oxylipin composition of lipoproteins in hypertriglyceridemic, statin-treated subjects. PloS one, 2014;9(11):e111471.
49. Zahedi H, Eghtesadi S, Seifirad S, Rezaee N, Shidfar F, Heydari I, Golestan B, Jazayeri S. Effects of CoQ10 supplementation on lipid profiles and glycemic control in patients with type 2 diabetes: a randomized, double blind, placebo-controlled trial. Journal of Diabetes & Metabolic Disorders. 2014 Dec;13(1):1-8.
50. Kashyap M. Mechanistic studies of high-density lipoproteins. The American journal of cardiology. 1998 Dec 17;82(12):42U-8U.
51. Mohseni M, Vafa MR, Hajimiresmail SJ, Zarrati M, Forushani AR, et al. Effects of coenzyme q10 supplementation on serum lipoproteins, plasma fibrinogen, and blood pressure in patients with hyperlipidemia and myocardial infarction. Iranian red crescent medical journal. 2014 Oct;16(10).
52. Gholami M, Rezvanfar MR, Delavar M, Abdollahi M, Khosrowbeygi A. Effects of coenzyme Q10 supplementation on serum values of gamma-glutamyl transferase, pseudocholinesterase, bilirubin, ferritin, and high-sensitivity C-reactive protein in women with type 2 diabetes. Experimental and Clinical Endocrinology & Diabetes. 2019 May;127(05):311-319.
53. Eriksson JG, Forsen TJ, Mortensen SA, Rohde M. The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus. Biofactors. 1999;9(2-4):315-318.
54. Zhang P, Yang C, Guo H, Wang J, Lin S, Li H, Yang Y, Ling W. Treatment of coenzyme Q10 for 24 weeks improves lipid and glycemic profile in dyslipidemic individuals. Journal of clinical lipidology. 2018 Mar 1;12(2):417-427.
55. Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, Nicholls MG, Scott RS, George PM. A randomized, double-blind, placebo-controlled crossover study of coenzyme Q10 therapy in hypertensive patients with the metabolic syndrome. American journal of hypertension. 2012 Feb 1;25(2):261-270.
56. Rosenfeldt FL, Haas SJ, Krum H, Hadj A, Ng K, Leong JY, Watts GF. Coenzyme Q 10 in the treatment of hypertension: a meta-analysis of the clinical trials. Journal of human hypertension. 2007 Apr;21(4):297-306.