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Effects of Therapeutic Lifestyle Change Diet and Q10 Plus L-Carnitine Supplementation on Inflammatory Biomarkers of In-Stent Restenosis, Lipid Profile, and Left Ventricular Ejection Fraction in Myocardial Infarction: A Randomized Clinical Trial

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Abstract

Background: Following Myocardial Infarction (MI) and percutaneous coronary intervention (PCI), the modification of cardiovascular risk factors and inflammation can improve MI progression and PCI outcomes. Up to now, no certain conclusions have been drawn regarding the effect of therapeutic lifestyle change (TLC) diet and a combination of Q10 plus L-carnitine (LC) supplementation on inflammatory biomarkers of In-Stent Restenosis (ISR), lipid profile, and Left ventricular ejection fraction (LVEF).
Objectives: This study aimed to evaluate the effects of TLC diet and Q10 plus LC supplementation on inflammatory biomarkers of ISR, lipid profile, and LVEF following MI and PCI.
Methods: This single-blind randomized controlled trial was conducted on 128 subjects. After randomization for treatment allocation, the subjects were divided into the study groups through block randomization. The MI patients were admitted to 2 hospitals, namely Al-Zahra and Kowsar (Shiraz, Iran), between April 2015 and May 2016. The patients were divided into 4 groups receiving TLC diet (A), oral Q10 150 mg/d and LC 1200 mg/d (B), a combination of LC plus Q10 and TLC diet (C), and the routine care (D). This study evaluated Interleukin-6 (IL-6) and high sensitive C-reactive protein (hs-CRP) as inflammatory biomarkers of ISR, lipid profile, and LVEF in 128 patients with MI undergoing PCI before and 3 months after the intervention.
Results: The results showed a significant decrease in hs-CRP in groups B (11.8 $\pm$ 4.3 to 2.0 $\pm$ 1 mg/L) and C (11.7$\pm$3.9 to 1.3$\pm$1.1 mg/L) ($P < 0.0001$ and $P < 0.0001$, respectively), but not in group A. Also, a significant reduction was found in IL-6 in groups A (38.0 $\pm$ 15 to 9.4 $\pm$ 2 pg/mL), B (34.6 $\pm$ 12 to 5.1 $\pm$ 2.4 pg/mL), and C (33.7 $\pm$ 12 to 4.8 $\pm$ 2.1 pg/mL) ($P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively). Additionally, LDL and total cholesterol, but not TG, levels significantly decreased in groups A (150 $\pm$ 17 to 80 $\pm$ 13 mg/dL), B (148 $\pm$ 15 to 77.2 $\pm$ 14 mg/dL), and C (142 $\pm$ 11 to 64.8 $\pm$ 10 mg/dL) ($P < 0.0001$, $P < 0.001$, and $P < 0.0001$, respectively). Nevertheless, only group C showed a significant improvement in LVEF (45.1 $\pm$ 8 to 53.6 $\pm$ 8) ($P < 0.027$).
Conclusions: An adjuvant therapy with TLC diet and supplementation with Q10 and LC seems to be required for secondary prevention following MI and PCI. TLC diet and Q10 plus LC appeared to be effective in inflammatory biomarkers of ISR as well as LDL reduction.

Keywords: Diet, Carnitine, CoQ 10, Myocardial Infarction, Percutaneous Coronary Intervention, Inflammation

1. Introduction

Following Myocardial Infarction (MI) and percutaneous coronary intervention (PCI), secondary prevention with modified lifestyle (1) and dietary supplement has been emphasized to modify cardiovascular (CV) risk factors and improve PCI outcomes (2, 3). After optimal cardio protective medication, the improvement of CV risk factors, such as hyperlipidemia and inflammation, can reduce the risk of consequent events and death, which in turn can affect public health and economic burden of the disease. Previous studies have shown that 47% of MI patients had hyperlipidemia (4). Additionally, an extreme inflammatory response was detected post MI, and the improvement of inflammation had an important role in ventricular remodeling and promotion of left ventricular ejection fraction (LVEF) (5). In addition, In-Stent Restenosis (ISR) is one of the important complications after PCI, which depends on CV risk factors (6, 7), such as inflammation (8), hyperlipidemia (9), and lesion features (10). A prior study indicated that

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ISR was common in patients undergoing PCI (6, 11). Therefore, the improvement of CV risk factors by safe adjuvant therapy, proper diet, and dietary supplementation seems to be required for improving secondary prevention in post MI patients undergoing PCI.

Inflammation, as a new CV risk factor, can affect restenosis after angioplasty and MI (12, 13). The new generation of drug-eluting stents (DESs) has been shown to be superior to Bare Metal Stents (BMS) due to reducing the risk of inflammation and ISR (6, 7). However, DESs are not immune to restenosis in the long run (6), and ISR is also common in DES generation (12% - 23.5%) (6, 11). In spite of heterogeneity across studies, evidence has indicated that plasma high-sensitivity C-reactive protein (hs-CRP) level, as an inflammatory biomarker, could predict coronary ISR after stenting at both admission and follow-up in patients (14-16). Interleukin-6 (IL-6), as an established inflammatory biomarker of atherosclerosis, could also predict coronary stenosis with high sensitivity and specificity (17, 18). Therefore, it is necessary to control inflammation to promote PCI outcomes. Despite the emerging role of inflammation in ISR, little is known about proper diets and dietary supplementations following PCI in the new guideline (2, 6).

Coenzyme Q10 (Q10) and L-carnitine (LC), as potent antioxidant dietary supplements, may affect MI progression (19, 20). There are conflicting research results about the effects of Q10 and LC on inflammatory markers (21-23), lipid profiles (24, 25), and LVEF (26, 27). Although coenzyme Q10 supplementation has been found to affect inflammatory markers in healthy subjects, few clinical studies have investigated the relation between coenzyme Q10 and inflammation in patients with MI. A study by Fotino et al. showed that Q10 supplementation had a significant effect on the improvement of LVEF in heart failure (26). Although the limited evidence has suggested that LC had no impacts on lipid profiles, a recent meta-analysis indicated that LC could have promising effects on lipid profiles in hemodialysis patients (28). Besides, another study indicated that LC supplementation could reduce inflammatory biomarkers (29). However, the effects of Q10 plus LC supplementation on inflammatory biomarker of ISR and LVEF have not been investigated yet.

On the other hand, lifestyle modification is also a simple but powerful method in secondary prevention of post MI patients undergoing PCI. Lifestyle changes should be focused on dietary interventions, weight management, smoking cessation, and regular physical activity. Therapeutic lifestyle change (TLC) diet program, as a specific regime for blood lipid lowering (30, 31), is mainly composed of the above-mentioned recommendations. Generally, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) can contribute to restenosis after PCI (9). High LDL levels are associated with increased incidence of coronary revascularization after PCI, and LDL/HDL ratio has an impact on long-term outcome in patients undergoing PCI (32). Additionally, studies showed that regular physical activity could affect inflammation post MI, reduce coronary restenosis, and improve LVEF (33, 34). However, a limited number of studies have been conducted regarding the effect of TLC diet program on inflammatory biomarker of ISR and MI progress.

As mentioned above, some studies indicated that both LC and Q10 have positive effects on LDL lowering, inflammation process, and LVEF. Nevertheless, the effects of the two supplements in a combination have not yet been investigated. In addition, far too little attention has been paid to the reduction of inflammation and modification of lipid profiles by dietary supplementation and TLC diet to improve PCI outcome. Thus, the present study aimed to evaluate the effects of TLC diet and Q10 plus LC supplementation on inflammatory biomarkers of ISR, lipid profiles, and LVEF.

2. Methods

2.1. Design and Sample Size

This was a single-blind randomized controlled trial with a 2*2 factorial design. Based on mean differences in LDL (25), 5% type I error, 80% power, and 20% probability of loss, a 128-subject sample size was determined for the study.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria of the study were: the first experience of Acute Myocardial Infarction (AMI) diagnosed based on the European society of cardiology/American college of cardiology (ESC/ACC) diagnostic criteria for AMI, age of 40 - 65 years, being candidate for primary PCI within 24 hours after MI, having low density lipoprotein (LDL) > 130 mg/dL (measured within 24 - 48 hours after MI), LVEF $\geq$ 30 pre procedure of PCI, receiving atorvastatin 80 mg daily, having no history of cardiac events after PCI , arrhythmia, and congestive heart failure, not having consumed warfarin and antioxidants such as vitamin C, E, and omega 3, not suffering from documented psychological diseases, and not having used any lipid lowering diet therapy in the previous six months. On the other hand, the exclusion criteria of the study were withdrawal from the study within 60 days after the intervention.

2.3. Sampling and Random Assignment

At first, the research population included 837 MI patients who were admitted to 2 specialized heart hospitals, namely Al-Zahra (governmental, specialized, referral heart hospital in south of Iran with 7 cardiac care units (CCUs)) and Kowsar (general, charity hospital with 3 CCUs), Shiraz, Iran, from April 2015 to May 2016. According to the inclusion and exclusion criteria of the study, 128 patients were selected, provided with a full explanation about the study objectives, and asked to sign written informed consent (Figure 1). Then, a 2-step simple randomization was used. After randomization for treatment allocation, they were divided into the study groups through permuted block randomization.

2.4. Intervention

The patients were divided into 4 groups each including 32 participants. The participants in the TCL diet group (group A) received TCL diet in accordance with their weight and individual characteristics. The participants in the supplement group (group B) received two supplements: LC 1200 mg (produced by Karen Company, Iran) and Q10 150 mg (produced by LYNAE Company, U.S.). It is noteworthy that the appropriate doses of supplements were derived from a previous study (21, 25). The participants in the TLC diet and supplement group (group C) received TLC diet and two supplements, namely LC 1200 mg and Q10 150 mg. Finally, the participants in the control group (group D) only received the routine care. All the patients were followed up for 3 months.

2.4.1. The TLC Diet Planning

First, a three-day dietary record was used to evaluate the patients' diet at baseline and at the end of the intervention. Using the NUT4 software (a computer program for performing nutritional calculations), we calculated energy and nutrients data of the three-day dietary records. Then, a 7-day TLC diet plan consisting of 3 meals and 3 snacks was designed, which had to be continued for 90 days. In addition, the patients were educated for 30 minutes and provided with an educational brochure. Accordingly, the TLC program (30, 31) included the following measures: 1) limiting the intake of Saturated Fatty Acids (SFA) (< 7% of total daily calories), cholesterol (< 200 mg/day), monounsaturated fatty acids (MUFA) (10% - 20%), and Polyunsaturated Fatty Acids (PUFA) (< 10%), 2) increasing phytosterols (comprising plant sterols and stanols) (2 servings per day) and water soluble fiber (10 - 25 g/day), 3) having moderate intensity physical activity for 20 minutes at least three times a week calculated by physical activity questionnaires (IPAQ) and, 4) cessation of smoking (13). The participants were visited on days 45th and 90th. It should be noted that the participants could contact the researcher through text massages if they had any concerns during the study period.

2.5. Measurements of Physical Activity

IPAQ is a valid and reliable instrument designed primarily for adults (age range of 15 - 69 years) in Iranian population (35). The IPAQ face-to-face interview format was used to assess the habitual physical activity during the previous 7 days before MI. Additionally, energy consumption was calculated based on the second edition of codes and Metabolic Equivalent (MET) values. The IPAQ data were converted to MET scores (MET-min per week) for each type of activity by multiplying the number of minutes dedicated to each activity class by the specific MET score for that activity. Moreover, based on the revised scoring protocol 2005, physical activity levels were categorized into 3 levels as follows: high (at least 3000 MET-minutes/week), moderate (at least 600 MET-minutes/week), and low (less than 600 MET-minutes/week) (36).

2.6. Biochemical Analysis

Blood samples were taken from each patient before and at the end of the intervention. After centrifugation, serum was separated and stored. Plasma lipids were measured in centralized nutrition laboratories by standard, validated methods. Concentrations of serum biomarkers were determined using an auto-analyzer (Biotechnical 1500, Rome, Italy). The concentrations of serum LDL, HDL, total cholesterol, and TG were measured through an enzymatic colorimetric assay method using commercial kits (Pars Azmoon, Iran). The equipment was calibrated using Centronics GmbH, Germany. Then, the results of each run test were checked according to the Centronics GmbH control.

Serum hs-CRP levels were measured in duplicate using commercial ELISA kits (Monobind, USA). Serum hs-CRP levels were expressed in mg/L and the sensitivity of this assay was found to be 0.2 mg/L. Besides, serum IL6 levels were measured using IL6 ELISA human kits (IBL Company, Ltd. Hamburg, Germany) according to the instruction manual. Serum IL6 levels were expressed in pg/mL using an 8-point calibration curve from 0 to 100 pg/mL. The calibration curve was obtained using multiple defined concentrations of CRP and IL6 calibrator in the kit. The CRP concentration in the sample was calculated by interpolation of the calibration curve. A monthly verification of the instrument's linearity was done using DRI-DYE check strips.

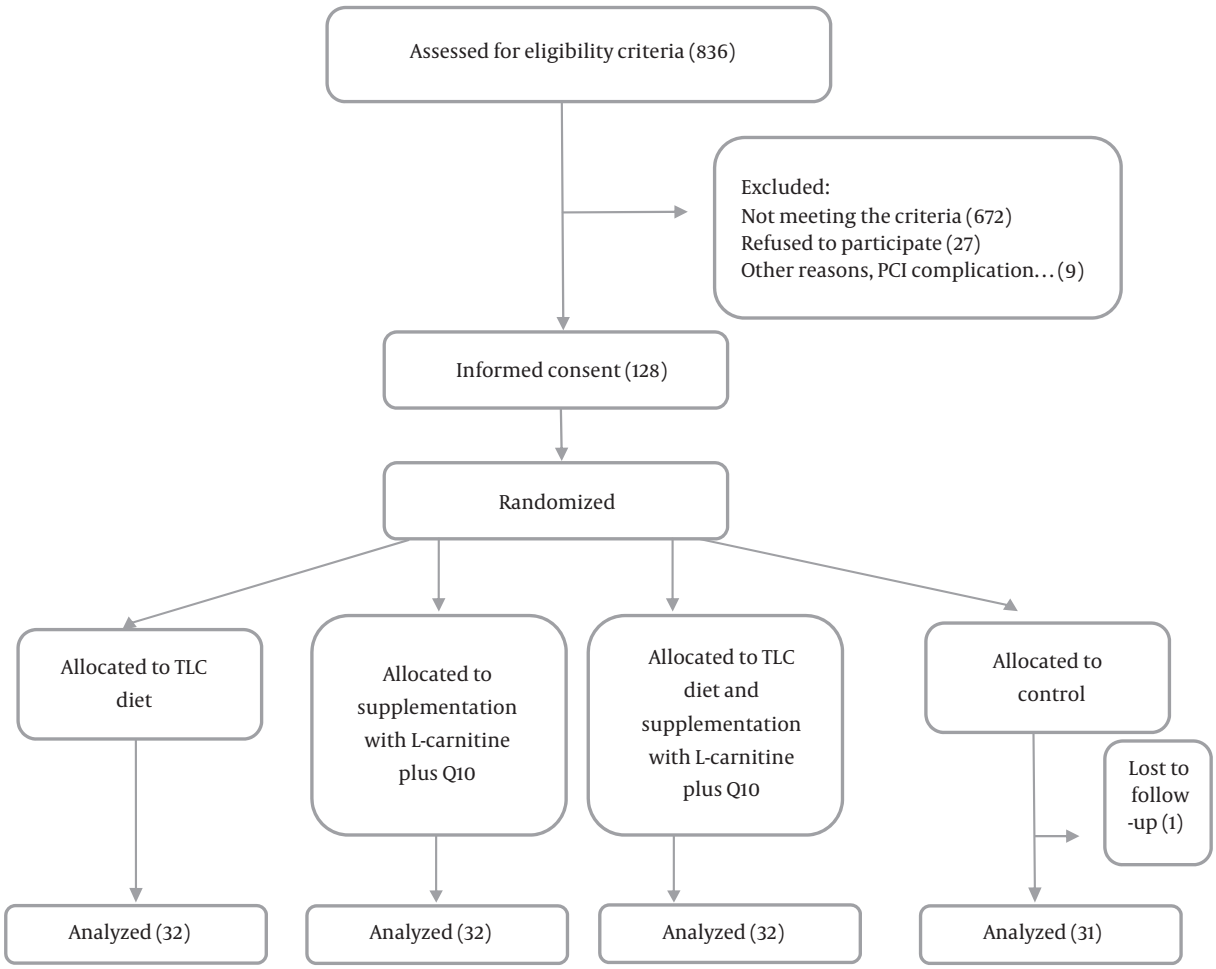

Figure 1. Consort Flow Diagram of Participants' Recruitment in the Study

2.7. Echocardiographic Measurements

Echocardiography was done by an expert cardiologist using an echocardiogram (General Electric Vivid-7 echocardiography machine, US) and a standardized imaging protocol. Indeed, LVEF was measured using the Teichholz formula (37) that has been approved previously.

2.8. Instrument

The study data were collected using a questionnaire including items regarding socio-demographic and clinical characteristics of patients, such as age, marital status, education level, history of diabetes, hypertension, and smoking, and number of vessel diseases in angiography report, before the intervention. Body weight was measured to the nearest 0.1 kg using a calibrated electronic scale. Body mass index (BMI) in kilograms per meters squared was also computed.

2.9. Ethical Issues

Approval for the study was obtained from ethics committee of Shiraz University of Medical Sciences where the study was carried out. All subjects provided written informed consent. The study was also registered in the Iranian registry of clinical trials (IRCT registration number: IRCT2282620150719N1).

2.10. Statistic

Continuous variables were expressed as mean ± standard deviation, while categorical ones were presented as absolute numbers and percentages. First, Kolmogorov-Smirnov test was used to assess normal distribution of the data. Then, paired ttest was used to compare the study variables before and after the intervention. Analysis of covariance (ANCOVA) was also employed to compare the four study groups regarding hs-CRP, IL-6, lipid profile, and LVEF.

It should be noted that the scores were adjusted based on the patients' weights. Moreover, paired ttest was used to compare dietary intake indices before and after the intervention. Besides, analysis of variance (ANOVA) was employed to analyze the effects of the dietary intervention. Finally, the relationships between socio-demographic variables and hs-CRP, IL6, LDL, HDL, TG, and total cholesterol levels were examined using linear regression analysis. All data analyses were performed using the SPSS statistical software (SPSS 19.0 by SPSS software Inc.) and p-values less than 0.05 were considered to be statistically significant.

3. Results

This study evaluated the effects of three interventions on hs-CRP, IL-6, lipid profile, and LVEF in MI and PCI participants. Out of the 830 patients screened for eligibility, 128 were enrolled in the research. All the participants performed the interventions and completed the follow-up period. The participants' socio-demographic and clinical characteristics are presented in Table 1. Accordingly, except for weight, no significant differences were found among the study groups in terms of age, sex, education level, cardiac risk factors, drug use, work status, LVEF, physical activity, and number of involved vessels. Among the participants, 91% were male and 98% were married. Additionally, the most frequently reported comorbidities were hypertension (34.3%), diabetes (27.3%), smoking (21.8%), obesity (6.2%), single vessel disease (64.5%), two-vessel disease (24.5%), and multi-vessel disease (11%). Also, 90.6% of the participants had ST-segment elevation MI (STEMI).

According to Table 2, no significant difference was found among the 4 study groups regarding dietary intake at baseline. The results indicated that the participants recruited in groups A (TLC diet) and C (TLC diet and supplementation with LC plus Q10) followed the instructions given by the research team and fulfilled TLC diet plan. The result also showed no significant changes in dietary intake in groups B (supplementation with LC plus Q10) and D (control).

Comparison of the four groups regarding hs-CRP, IL-6, lipid profile, and LVEF before and after the intervention has been made in Table 3. As can be seen, all variables significantly changed in the 3 intervention groups and the control group before and after the 3-month follow-up. However, the results of post hoc analysis revealed a significant difference among the 4 groups regarding all the variables, except for TG concentration ($P < 0.632$).

The mean differences of hs-CRP, IL-6, and LVEF with SEM have been indicated in 3 parts in Figure 2. The hs-CRP part illustrated no significant differences between groups A and D ($P < 0.723$). In addition, groups B and C were significantly different from group D ($P < 0.001$ and $P < 0.0001$, respectively). The IL-6 part of Figure 2 shows that this measure significantly decreased in groups A, B, and C compared to the control group (all $P < 0.0001$). However, no significant differences were found between groups A and B ($P < 0.092$), groups A and C ($P < 0.176$), and groups B and C ($P < 0.738$). Finally, considering LVEF, the results showed no significant differences between groups A and B, and D. Nonetheless, group C was significantly different from groups A ($P < 0.043$), B ($P < 0.007$), and D ($P < 0.011$).

The mean differences of LDL, cholesterol, HDL, and TG with SEM among the 4 groups have been presented in 4 parts in Figure 3. Considering LDL level, a significant difference was observed between group C and groups A ($P < 0.001$), B ($P < 0.001$), and D ($P < 0.0001$). However, there was no significant difference between groups A and B in this regard ($P < 0.360$). With respect to cholesterol level, group C was significantly different from groups A ($P < 0.001$), B ($P < 0.001$), and D ($P < 0.001$). The results also showed a significant difference between groups A and C, and group D concerning HDL level ($P < 0.031$). However, no significant differences were found among the four groups regarding TG level.

Finally, the results of MET-week analysis revealed no significant differences in groups A and C after three months ($P < 0.117$ and $P < 0.227$, respectively). The results of linear regression analysis also showed no significant relationships between socio-demographic variables and hs-CRP, IL6, LDL, HDL, TG, and total cholesterol levels. For management of space, the details have not been mentioned.

4. Discussion

To our knowledge, this is the first study investigating the effects of TLC diet and dietary supplementation with Q10 plus LC on hs-CRP, IL-6, lipid profile, and LVEF in post MI patients undergoing PCI. Although the new generation of DES decreases inflammation and restenosis, ISR is still common and has a negative impact on PCI outcomes. Therefore, an additional adjuvant therapy seems to be required for secondary prevention. The present study aimed to determine the effect of TLC diet and supplement therapy on inflammatory biomarkers of ISR and lipid profiles so as to facilitate the development of secondary prevention.

The findings of this clinical trial demonstrated that supplementation with Q10 plus LC, but not TLC diet, had a significant effect on decreasing hs-CRP among the MI patients. On the other hand, TLC diet, Q10 plus LC supplementation, and the combination of the 2 interventions had nearly the same significant effect on decreasing IL-6. The findings also revealed the synergistic effect of TLC diet and supplementation with Q10 plus LC on the improvement of

Table 1. The Participants' Socio-Demographic and Clinical Characteristics[a]

	Group 1 (N = 32)	Group 2 (N = 32)	Group 3 (N = 32)	Group 4 (N = 31)	P Value
Age, y	50 ± 10	54 ± 8	51 ± 9	51 ± 10	0.28
Gender (male)	90.6 (29)	87.5 (28)	84 (27)	81.2 (26)	0.75
Marital status, %					
Married	93.7 (30)	90.6 (29)	87.5 (28)	87.5 (28)	0.86
Single	6.2 (2)	9.3 (3)	9.3 (3)	6.2 (2)	
widowed	0	0	3.1 (1)	3.1 (1)	
Education status					
Below high school	56.2 (18)	50.0 (16)	46.8 (15)	50 (16)	0.18
High school	25.0 (8)	31.2 (10)	28.1 (9)	25 (8)	
Academic	18.7 (6)	18.6 (6)	25.0 (8)	21.8 (7)	
One-vessel disease	62.5 (20)	65.6 (21)	62.5 (20)	65.6 (21)	
Two-vessel disease	25.0 (8)	28.1 (9)	21.8 (7)	21.8 (7)	0.98
Multi-vessel disease	12.5 (4)	6.2 (2)	15.6 (5)	9.3 (3)	
History of hypertension	34.3 (11)	37.5 (12)	31.2 (10)	34.3 (11)	0.94
History of diabetes mellitus	28.1 (9)	31.2 (10)	21.8 (7)	28.1 (9)	0.98
Smoker	21.8 (7)	31.2 (10)	18.7 (6)	28.1 (9)	0.88
Obesity, BMI (kg/m^2) > 30	9.3 (3)	6.2 (2)	3.1 (1)	6.2 (2)	0.19
LVEF	45 ± 9.3	42 ± 8.7	46 ± 9.3	46 ± 7.6	0.13
STEMI	90.6 (29)	87.5 (28)	90.6 (29)	93.7 (30)	0.20

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; STMI, ST elevation myocardial infarction.
[a]Values are expressed as % (No.) or mean ± SD.

Table 2. The Participants' Dietary Intake and Physical Activity Before and After the Intervention[a]

Parameter	Groups												P Value[b]
	A (n = 32)			B (n = 32)			C (n = 32)			D (n = 31)			
	Before	After	P Value[c]	Before	After	P Value[c]	Before	After	P Value[c]	Before	After	P Value[c]	
SFAs, %	13	7	0.04	14	12.5	0.14	13	8	0.01	14	13	0.23	0.0001
MUFAs, %	7.5	12.8	0.02	8	8.3	0.23	7.6	13	0.003	7.2	8.1	0.35	0.0001
PUFAs, %	14.5	9.5	0.003	15	14	0.67	14	10	0.042	13.6	14	0.44	0.0001
Cholesterol, mg/dL	238 ± 11	162 ± 19	0.0001	243 ± 16	238 ± 19	0.055	247 ± 18	160 ± 26	0.0001	236 ± 14	231 ± 19	0.07	0.0001
Water soluble fiber intake, g/d	7 ± 20.7	18 ± 3.1	0.0001	7 ± 2.2	7 ± 10.8	0.286	8 ± 3.0	18 ± 4.0	0.0001	7 ± 0.2.6	7 ± 20.4	0.44	0.0001
Physical activity, MET/min	368 ± 73	518 ± 84	0.0001	367 ± 67	388 ± 81	0.108	396 ± 78	573 ± 101	0.0001	368 ± 72	388 ± 89	0.11	0.0001

Abbreviations: MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFA, saturated fatty acids.
[a] Group A, TLC diet; Group B, supplementation with Q10 plus L-carnitine; Group C, supplementation with Q10 plus L-carnitine and TLC diet; Group D, control.
[b] ANOVA p-value after the intervention.
[c] Paired t-test p-values calculated based on mg/day for SFAs, MUFAs, and PUFAs.

LVEF. Another important finding was that TLC diet as well as supplement therapy with Q10 plus LC was significantly effective in decreasing LDL and cholesterol levels, while they had no significant effect on TG level. On the other hand, only TLC diet led to an improvement in HDL level.

This section has been classified under 3 headings as follows: the effect of TLC diet, the effect of Q10 plus LC supplementation, and the effect of TLC diet and Q10 plus LC supplementation on hs-CRP and IL-6, lipid profile, and LVEF.

4.1. The Effect of TLC Diet Intervention

The effect of TLC diet on lowering LDL level has been established in previous studies (30). In fact, TLC diet is a specific dietary approach to improve CV risk factors. Many patients with hyperlipidemia could achieve the intended LDL levels without medications within 12 weeks of initiating

Table 3. Comparison of Changes in the Study Groups' Inflammatory Markers, Lipid Profiles, and Ejection Fractions Before and After the Intervention[a]

Parameters	Group A (n = 32)			Group B (n = 32)			Group C (n = 32)			Group D (n = 31)			P Value[b]
	Before	After	P Value[c]	Before	After	P Value[c]	Before	After	P Value[c]	Before	After	P Value[c]	
hs-CRP, mg/L	11.3 ± 3.8	2.9 ± 0.78	0.0001	11.8 ± 4.3	2.0 ± 1.1bad	0.0001	11.7± 3.9	1.3 ± 1.1	0.0001cad	10.9 ± 3.7	3.0 ± 1.2	0.0001	< 0.0001
IL6, pg/mL	38.0 ± 15.6	9.4 ± 2.0ad	0.0001	34.6 ± 12.0	5.1 ± 2.4bd	0.0001	33.7 ± 12	4.8 ± 2.1cd	0.0001	32.9 ± 8.4	9.2 ± 2.5	0.0001	< 0.0001
E.F, %	44.2 ± 7.9	49. 1 ± 7.2	0.0001	43.3 ±9.2	47.6 ± 9.5	0.0001	45.1 ± 8.0	53.6 ± 8.2cabd	0.0001	45.2 ± 7.1	47.0 ± 10.1	0.0001	< 0.027
LDL, mg/dL	150.1 ± 17.1	80 ± 13.0ad	0.0001	148 ± 15.5	77.2 ± 14.5bd	0.0001	152 ± 17.3	64.8 ± 10.2cabd	0.0001	142 ± 11.5	102 ± 7.1	0.0001	< 0.0001
HDL, mg/dL	38.9 ± 5.6	41.8 ± 5.7	0.0001ad	38.9 ± 5.7	40.5 ± 5.6	0.013	39.6 ± 6.9	41.8 ± 6.6	0.0001cd	36.8 ± 4.3	38.1 ± 4.2	0.0001	< 0.031
TG, mg/dL	177 ± 21.6	115 ± 21.6	0.0001	177 ± 30	112.3 ± 21.4	0.0001	185 ± 51	109 ± 19	0.0001	171 ± 24	110 ± 20	0.0001	< 0.607
CHO, mg/dL	222.2 ± 14.1	144.8 ± 15.5ad	0.0001	222.5.0 ± 16.5	141.8 ± 17.4	0.0001	226.5 ± 18.4	128.0 ± 11. cabd	0.0001	215.7 ± 14.8	165 ± 10.4	0.0001	< 0.0001

[a] Values are expressed as mean ± SD.
[b] ANCOVA P value after adjustment for weight and after intervention. P Significance < 0.05 in between-groups (groups A, B, C and D presented with a, b, c and d). Group A, TLC diet; Group B, supplementation with Q10 plus L-carnitine; Group C, supplementation with Q10 plus L-carnitine and TLC diet; Group D, control.
[c] Paired t-test P value.

the TLC diet (38). In accordance with the previous findings, the current study results showed that TLC diet was effective in lowering LDL level (39). It is notable that acquiring a higher 50% decrease in LDL is accompanied by better clinical outcomes after MI (40). Lower LDL levels also played a critical role in preventing coronary restenosis (9). Thus, TLC diet along with statin therapy could promote LDL management and probably decrease the chance of restenosis related to high LDL levels. The findings of the present study also revealed that TLC diet could increase HDL level by 6%, which is consistent with other researches reporting that TLC diet resulted in a 4% increase in HDL level (31). These results might be attributed to statin effect, increased Monounsaturated Fatty Acids (MUFA) in TLC diet, and exercising. Our results also demonstrated that the percentage of changes in LDL, cholesterol, HDL, and TG levels in groups A and C that received the TLC program was higher compared to similar studies (31). Yet, comparing these results with similar studies must be interpreted with caution because all our study participants had hyperlipidemia and received statin.

Previous studies indicated that dietary interventions could decrease hs-CRP and IL-6 levels (41). However, to our knowledge, changes in hs-CRP and IL-6 levels due to TLC diet have not been identified in MI. In the current study, TLC diet had no significant effects on decreasing hs-CRP, which is in contrast to the results of a previous research conducted on diabetic patients (34, 42).

This might be justified by the fact that statins have anti-inflammatory properties (43). Besides, our results indicated that TLC diet significantly decreased IL-6 levels, which is in line with the results of earlier studies conducted on the issue (44). Yet, further studies are suggested to focus on the long-term effects of TLC diet and exercising on inflammatory biomarkers of ISR.

In the current study, TLC diet had no significant effects on LVEF. Generally, most patients' ejection fraction tends to improve after MI. However, the degree of improvement in LVEF may be influenced by many factors, such as location of infarction and coronary artery features (45).

4.2. The Effect of Q10 Plus LC Supplementation

Q10 (25, 26) and LC (46) have been used in different heart diseases for decades. Indeed, different mechanisms have been reported for the role of Q10 and LC in hs-CRP, IL-6, lipid profiles, and LVEF in various medical conditions. Q10 plays an essential role in mitochondria electron transport chains for energy production. It could also protect the cardiac tissue from ischemia and reperfusion injury by increasing aerobic energy production that can help improve LVEF (45). Besides, Q10 has antioxidant and membrane stabilizing properties in the cardiac tissue and therefore, can help improve ejection fraction (47). It also possesses anti-inflammatory properties, which can decrease CRP and IL-6 levels. Moreover, LC is involved in energy metabolism and, due to its antioxidant properties, may be effective in decreasing inflammation. Myocardium tissue has one of the highest intracellular carnitine concentrations. It should be noted that myocardial carnitine levels are rapidly reduced during MI, and LC supplementation has been revealed to replace depleted myocardial carnitine levels, improve ejection fraction (48), and relieve angina symptoms (46). LC can also upturn mitochondrial transport of fatty acids and reduce availability for triglycerides synthesis that is effective in lipid profiles (24).

In general, hs-CRP and IL-6 play an evolving role in risk assessment after stent implantation (13). Additionally, plasma hs-CRP level may independently predict ISR

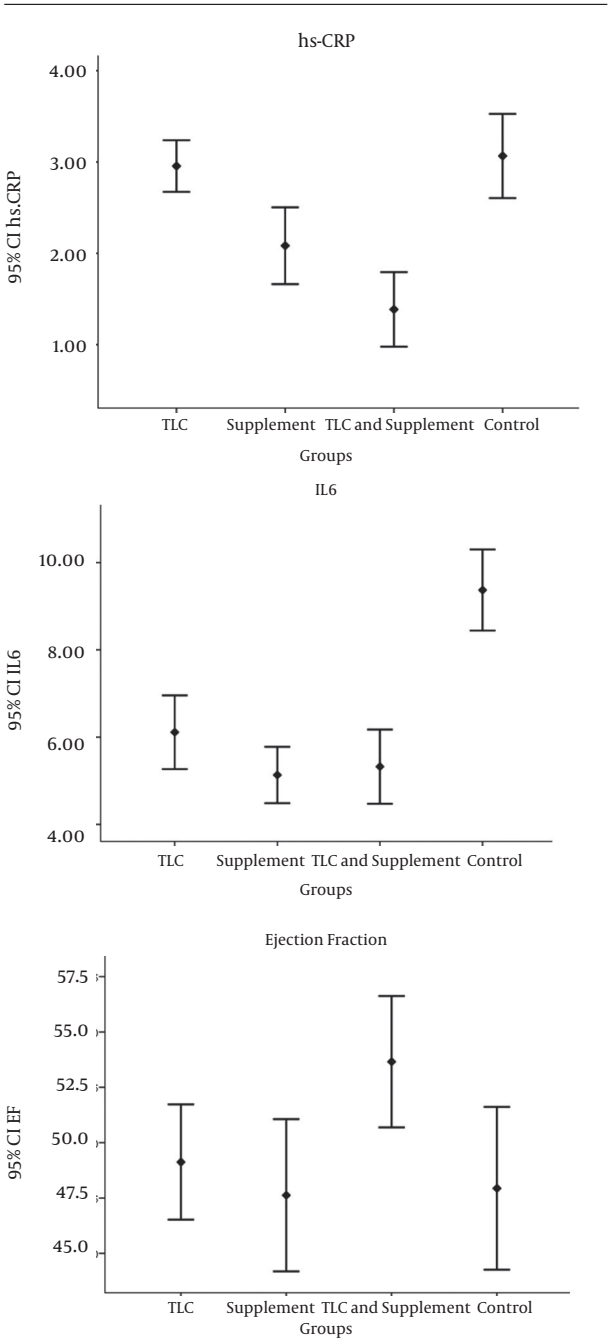

Figure 2. Mean Differences of hs-CRP, IL-6, and Ejection Fraction with Confidence Interval

at both admission and follow-up after DES implantation (49). The results of a meta-analysis also demonstrated a significant relationship between hs-CRP level and risk of ISR after successful coronary stenting (16). IL-6 is also one of the inflammatory markers that promote atherosclerosis development and plaque rupture (17). After MI, especially STEMI, patients tended to experience a rise in hs-CRP and IL-6 plasma levels that contributed to poor prognosis (50). In the present study, 81% of the patients experienced STEMI with high levels of hs-CRP and IL-6. The results revealed that supplementation with Q10 plus LC significantly reduced hs-CRP and IL-6 levels. In contrast, some studies disclosed a 14% decrease in IL-6 levels after supplementation with Q10 150 mg/d, and no significant change in hs-CRP levels (22). Previous studies also showed that IL-6 and CRP levels decreased significantly after LC supplementation (1000 mg/d) in patients with coronary artery disease (21). These results can possibly be explained by the synergistic effect of supplementation with Q10 plus LC on decreasing the inflammatory markers. Patient-related factors, such as sex (male), hypertension, age (46 - 60 years), and STEMI type, are also important variables that affect the inflammatory biomarkers (12). As mentioned in the "results" section, 35% of our study participants had the history of hypertension, 70% aged 45 - 60 years, and 91% were male. Therefore, it is logical to use safe dietary supplementations for decreasing inflammatory biomarkers in ISR.

The results of the present study showed that supplementation with Q10 plus LC significantly reduced LDL, cholesterol, and HDL, but not TG, levels. These results are consistent with those of the study by Stalin et al. which indicated that the combination of Q10 and atorvastatin decreased serum cholesterol and LDL levels and increased serum HDL level (25). Similarly, Bor-Jen Lee et al. performed a meta-analysis and revealed the positive effect of LC on LDL level (24, 28). However, Shojaei et al. used a combination of LC (1000 mg) and Q10 (100 mg) in hemodialysis patients and showed that the therapy had no significant effects on improvement of lipid profiles (51). This might be attributed to the patients' renal disease.

In addition, the current study findings revealed that Q10 plus LC had no significant effects on LVEF. On the contrary, some studies have demonstrated that Q10 or LC could improve LVEF. The results of a meta-analysis also speculated that Q10 had a significant effect on improvement of LVEF (pooled mean net change of 3.67% in heart failure) (26). On the other hand, some studies found no significant relationships between Q10 or LC and improvement of LVEF (20), implying that the effectiveness of Q10 may be reduced with concomitant use of the cardio protective medications (52).

4.3. The Effect of Combined TLC Diet and Supplementation Therapy

The findings of the current study disclosed that neither combined LC and Q10 nor TLC diet was significantly effective in LVEF. Nevertheless, the most important clinically rel-

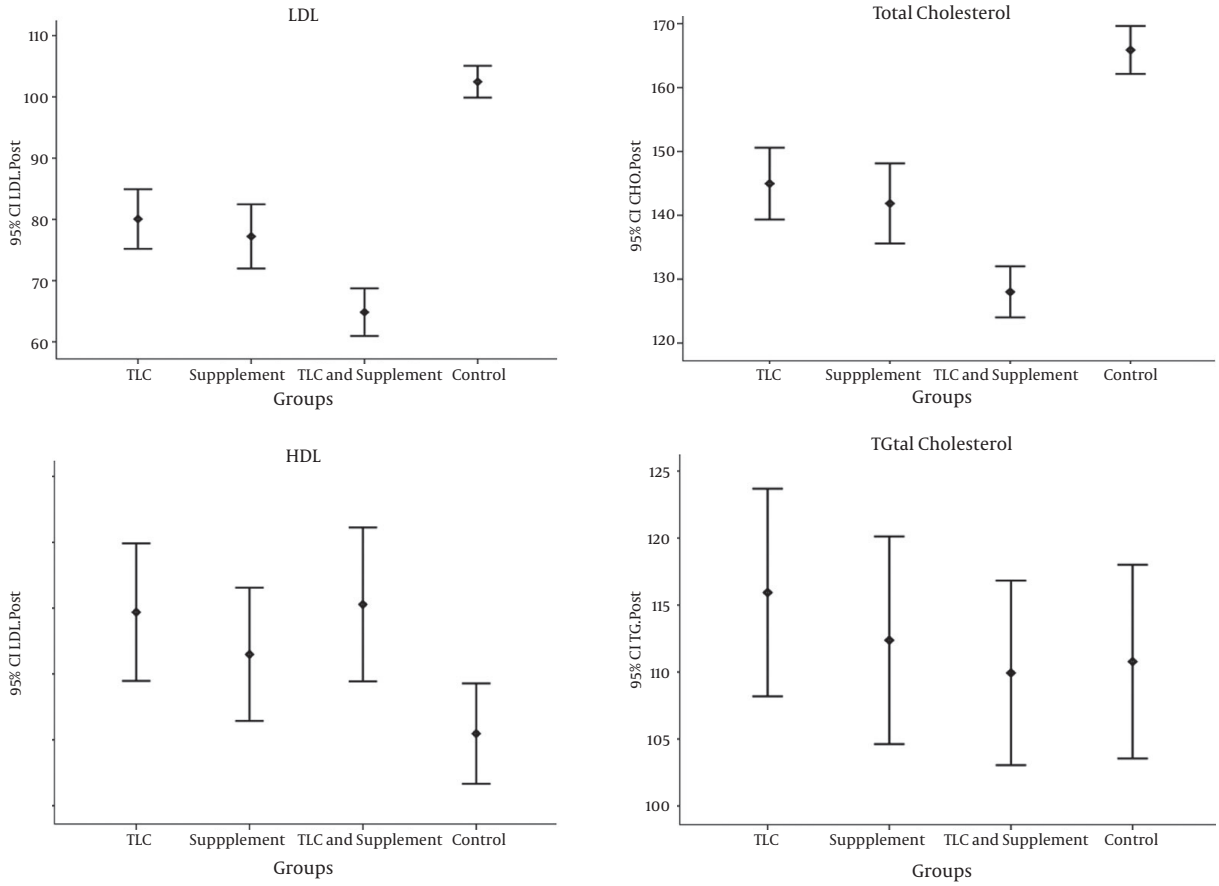

Figure 3. Comparison of the Mean Differences of LDL, Cholesterol, TG, and HDL with Confidence Interval

evant finding of the present study was the significant effect of the combination of TLC diet and supplementation with LC plus Q10 on the enhancement of LVEF. However, this result has not been previously described in other studies and need to be confirmed by further researches with larger sample sizes.

Moreover, our study results revealed that LC plus Q10 as well as TLC diet had a positive effect on lowering LDL and cholesterol levels. The combination of Q10 plus LC supplementation and TLC diet also had synergistic effects on LDL reduction. However, the researchers could not find any similar studies to compare the results.

Study Strengths and Limitations: The major strength of this study was the high response rate obtained from a well-designed clinical trial (Figure 1). Yet, this study had two limitations. First, this study only examined MI patients with hyperlipidemia within 3 months, which necessitates caution in interpretation of the results. Additionally, cardiac MRI is the best tool for measuring LVEF, and imaging single photon emission computed tomography (SPECT) is another viable option. Due to financial problems, conventional echocardiography was used in this study, which underestimates the left ventricular mass when using the Teichholz formula (53).

4.4. Conclusions

The main goal of the current study was to determine the impact of TLC diet, Q10 plus LC supplementation, and a combination of the two interventions on inflammation biomarkers of ISR, lipid profiles, and LVEF following PCI and MI. The most obvious finding of this study was that supplementation with Q10 plus LC had a significant effect on decreasing hs-CRP, IL-6, LDL, and cholesterol levels, while TLC diet showed no considerable effects on hs-CRP levels. The second major study finding was that the combination of Q10 plus LC and TLC diet significantly enhanced LVEF.

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Footnotes

Competing Interests: The authors declare that they have no competing interests.

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