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Cardiometabolic responses to L-carnitine in obese women with knee osteoarthritis: a randomized, double-blind, placebo-controlled pilot study

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Summary. This study aimed to investigate cardiometabolic responses to L-carnitine in obese women with knee osteoarthritis (OA). In this randomized double-blind, placebo-controlled trial, 50 obese women with mild to moderate knee OA were randomly allocated into 2 groups to receive 750 mg/d L-carnitine or placebo for 8 weeks. Anthropometric indices, blood pressure and atherogenic indices were measured before and after the intervention. Only 48 patients (23 in the L-carnitine group and 25 in the placebo group) completed the study. L-carnitine resulted in significant reduction in hip circumference (115.15±6.19 vs 113.57±4.89) compared with baseline (P=0.013); whilst it didn't change body mass index, waist circumference, waist to hip and waist to height ratios significantly (P>0.05). L-carnitine led to significant reduction in systolic blood pressure compared with placebo group, adjusted for baseline values (P=0.020). Atherogenic indices didn't change significantly in both groups through the study (P>0.05). No significant differences were observed in anthropometric measures and atherogenic indices between two groups after adjusting for baseline values and covariates (P>0.05). In conclusion, L-carnitine did not lead to significant changes in obesity-associated parameters and atherogenic indices in women with knee OA. However, long-term studies with higher doses of L-carnitine are needed to explore its efficacy as an anti-obesity and anti-atherogenic agent in OA patients.

Key words: L-carnitine, knee osteoarthritis, cardiometabolic status, women.

Introduction

Osteoarthritis (OA) is the most common adult joint disease that can develop in any joint in the body, but knees are one of the most commonly affected joints because they are the primary weight-bearing joints of the body (1, 2). The prevalence of this debilitating disease is higher in women than in men (3). The origin of the disease is unknown but obesity, joint injury, metabolic diseases, bone and joint malfunctions, genetic factors and age have been implicated (2).

Obesity represents a significant risk factor for OA and is typically accompanied by an increase in the risk factors of cardiovascular disease (CVDs) including dyslipidemia, hypertension, atherosclerosis and other metabolic disorders (4). Furthermore, OA patients are at higher risk than the general population for developing several additional serious conditions and CVDs in particular (5). Therefore, a therapeutic approach aiming to control body weight, might help prevent CVDs. Furthermore, epidemiological studies have indicated that patients with OA have altered levels of serum glucose and lipids, mainly in the form of increased concentration of serum total cholesterol (5-7). These data suggest that hypercholesterolemia and blood glucose are associated with unilateral and bilat-

eral knee OA independent of obesity. Therefore, it can be concluded that OA has an important systemic and metabolic component in its etiology (8). A more recent analysis of NHANES III data comprising a representative sample of 7,714 subjects demonstrated that each of the five cardiovascular risk factors that each comprises metabolic syndrome was more prevalent in the OA population than the population without OA (9).

Currently there is no apparent cure for OA; Common therapies include lifestyle modifications and pharmacologic agents. Conventional drug treatments include analgesics, anti-inflammatory agents, hyaluronic acid, and intra-articular glucocorticoids (10). To avoid the cardiac risks and gastrointestinal complications associated with traditional OA treatments particularly with long-term use (11,12), there has been a focus on complementary and alternative medicines recently, especially nutritional supplements. L-carnitine is a dietary supplement that plays an important role in shuttling the long-chain fatty acids across the inner mitochondrial membrane for βoxidation and ATP production (13). Existing data from human studies showed that L-carnitine may have cardiometabolic effects in patients with type 2 diabetes and non-alcoholic steatohepatitis (14,15). Recently, L-carnitine was reported to be effective in management of OA due to its anti-nociceptive and anti-inflammatory effects (16-18).

Owing to the growth of obesity and increase in prevalence of OA, and since there is no clinical trial investigating the effect of L-carnitine on cardiometabolic risk factors in OA patients, we hypothesized that supplementation with L-carnitine may have a positive effect on metabolic factors in OA patients. Therefore, this study was aimed to evaluate the effects of L-carnitine supplementation on cardiometabolic status in obese women with knee osteoarthritis (OA).

Materials and Methods

Subjects

In this randomized, double-blind, placebo-controlled pilot study, fifty volunteer women aged 40–60 years with the diagnosis of mild to moderate bilateral primary knee OA according to the American College of Rheumatology criteria (19,20) and body mass index (BMI) of 30–40 kg/m^2 were recruited from the rheumatology clinic of Tabriz University of Medical Sciences between November 2013 and November 2014. Subjects who had secondary OA (due to a known disorder), surgery, or a joint injection of the target knee within the past 6 months, any serious systematic disease, cardiovascular disease, diabetes mellitus, liver, renal and/or thyroid disorders and any other chronic inflammatory disease, pregnancy and lactation, smoking, alcohol intake, currently taking omega-3-fatty acids (e.g., fish oil) and antioxidant supplements, use of NSAIDs two weeks prior to and during the intervention were excluded. The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (Iran) and written fully informed consent was signed by all subjects before participating in the study. The trial has been registered at Iranian Registry of Clinical Trials website (code: IRCT201311231197N17).

Study design

The eligible participants were randomly divided into the intervention and placebo groups based on random block procedure consisting of 4 subjects per block, which matched subjects to each block based on menopausal status and age. The experimental group (n=25) received 3 tablets per day of L-carnitine tartrate supplement (750 mg/day), and placebo group (n=25) received 3 tablets per day of placebo. The supplements and placebo tablets were identical in appearance and were obtained from *Karen Pharmaceutical & Nutrilife Pharmaceutical* Co. (Yazd, Iran). The intervention period was 8 weeks, and subjects were followed by weekly phone contact during this time. The participants were asked to keep their usual dietary intake and physical activity during the study period.

Anthropometric measurements

At the beginning and at the end of the intervention period, body weight was measured to the nearest 0.5 kg using a Seca scale (Hamburg, Germany), with the patients being barefoot and wearing light clothing. Height was also measured using a mounted tape, with the participants' arms hanging freely by their sides and recorded to the nearest 0.5 cm. Body mass index was calculated by dividing weight (in kilograms) by the square of height (in meters) (21). Waist circumference

(WC) was obtained using an inelastic tape measure to the nearest 1 mm. The mid-point between the last rib and the iliac crest was recorded as WC. Hip circumference (HC) was measured at the widest point of the hip. The waist to hip (WtH) and waist to height ratios were calculated.

Blood pressure measurement

After a 5 minute rest, blood pressure was measured twice in the sitting position using a sphygmomanometer (Microlife, AG 1–10 model, Switzerland) and the average of the values was reported.

Physical activity and Dietary intake assessment

Physical activity levels of the patients were assessed using the short form of the International Physical Activity Questionnaire by an instructed interviewer before and at the end of study (22). The patients were classified as having high, moderate, or low physical activity levels according to the categorical scoring protocol of the short form of International Physical Activity Questionnaire (23). Information on food intake was collected by using a 24-hour recall method for 3 days (including 2 working days and 1 weekend) a week before and at the end of supplementation. Dietary intake of subjects was analyzed with the Nutritionist IV software program (First Databank Inc, Hearst Corp, San Bruno, CA, USA).

Biochemical measurements

At the beginning and at the end of the trial period, 5 mL of venous blood samples was collected after 12-hour overnight fasting. The serum samples were separated from whole blood by centrifugation and were kept at −80°C until biochemical analysis. Fasting Blood Sugar (FBS) and serum total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using the standard enzymatic colorimetric method by Bionik Diagnostic Kits (Tehran, Iran). Serum low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein (VLDL) levels were calculated using the Friedewald equation (24) and dividing TG by 5 (25), respectively. Finally, atherogenic indices (Log TG/HDL-C, LDL-C/HDL-C, and TC/HDL-C ratios) were calculated.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 software (SPSS, Inc., Chicago, IL). Normal distribution of data was verified with the Kolmogorov-Smirnov test and the descriptive data were reported as means and standard deviations. Comparisons between the baseline and final results for the measures within each group were made with the use of paired *t*-test. The independent sample *t*-test was used to compare the differences between variables between the two groups at baseline. Analysis of covariance (ANCOVA) was used to identify any differences between the two groups at the end of the study, adjusting for baseline values and covariates (duration of OA and changes of weight and calorie intake). *P*-value < 0.05 was considered as statistically significant.

Results

Fifty participants were recruited in the study. Finally 48 patients (23 in the L-carnitine group and 25 in the placebo group) completed the trial. Two subjects in the L-carnitine group were withdrawn due to discontinuing intervention (poor compliance with study protocols) and lost to follow-up (personal reason). The means ± SD age and disease duration of the participants were 51.56±6.24 and 4.63±4.19 years in the L-carnitine group and 52.60±7.10 and 6.28±6.24 years in the placebo group, respectively. There were no significant differences in mean age and disease duration between the study groups.

As indicated in Table 1, in comparison with baseline, total energy intake decreased significantly (P=0.011) in the L-carnitine group by 8.69% (1893.83 vs 1729.09). At the end of the study, results of ANCOVA test did not show statistically significant differences between the two groups in total energy intake, adjusted for baseline values (P>0.05). Moreover, no significant differences were found in physical activity level between the study groups at baseline and at the end of the study (P>0.05).

Table 2 presents the anthropometric measures and blood pressure of participants throughout the study. No significant changes were seen between and within groups in weight, BMI, WC, waist to hip and waist to

Table 1. Comparison of dietary intake in the L-carnitine group with the placebo group at baseline and after the intervention

Variable		L-carnitine group (n=23)	Placebo group (n=25)	Mean Difference (95%CI)	*P***
Energy (kcal/day)	Baseline	1893.83±366.87	1838.00±424.93	55.82 (-170.33, 281.98)	0.622
	After 8 weeks	1729.09±453.67	1786.61±450.07	-93.43 (-306.23, 119.37)	0.382
	*P**	0.011	0.567		
Carbohydrate (g/day)	Baseline	299.13±74.34	292.20±75.59	6.92 (-35.50, 49.35)	0.744
	After 8 weeks	267.55±78.99	279.26±87.01	-15.67 (-56.66, 25.31)	0.446
	*P**	0.010	0.472		
Protein (g/day)	Baseline	64.26±12.78	62.46±12.41	1.79 (-5.31, 8.91)	0.614
	After 8 weeks	65.99±15.77	61.59±16.28	3.53 (-4.98, 12.04)	0.409
	*P**	0.626	0.770		
Fat (g/day)	Baseline	52.24±16.99	50.18±15.75	2.06 (-7.16, 11.29)	0.655
	After 8 weeks	46.64±15.91	50.71±18.42	-5.07 (-13.90, 3.76)	0.254
	*P**	0.128	0.878		
SFA (g/day)	Baseline	12.96±5.03	11.82±4.53	1.13 (-1.55, 3.82)	0.401
	After 8 weeks	11.56±5.04	12.72±6.21	-1.61 (-4.72, 1.49)	0.301
	*P**	0.203	0.491		
MUFA (g/day)	Baseline	15.07±7.13	14.29±7.03	0.78 (-3.21, 4.79)	0.694
	After 8 weeks	13.14±6.18	14.77±7.08	-2.01 (-5.29, 1.26)	0.222
	*P**	0.126	0.735		
PUFA (g/day)	Baseline	15.15±5.29	14.51±5.81	0.63 (-2.52, 3.80)	0.686
	After 8 weeks	12.85±5.14	14.24±6.67	-1.63 (-4.85, 1.58)	0.312
	*P**	0.125	0.815		

SFA, Saturated fatty acid; MUFA, Mono unsaturated fatty acid; PUFA, Poly unsaturated fatty acid.
Values are means ± SD.
P < 0.05 was considered significant.
** P values indicate comparison within groups (paired t-test).*
*** P values indicate comparison between groups (Independent sample t-test at baseline and ANCOVA test, adjusted for baseline values, after 8 weeks).*

height ratios after 8 weeks of intervention (P>0.05). HC decreased significantly in the L-carnitine group by 1.37% (P=0.013); whilst results of ANCOVA test did not show statistically significant differences between the two groups in HC at the end of the study (P>0.05), adjusted for baseline values (Table 2). Although no significant changes were seen within groups in systolic blood pressure after 8 weeks of intervention (P>0.05), results of ANCOVA test showed statistically significant differences (P=0.020) between the two groups at the end of the study, adjusted for baseline values (Table 2). Furthermore, diastolic blood pressure did not change significantly after 8 weeks of L-carnitine supplementation (P>0.05); whilst it increased significantly in placebo group by 6.8%. Results of ANCOVA test did not show statistically significant differences between the two groups in diastolic blood pressure at the end of the study, adjusted for baseline values (Table 2).

As shown in Table 3, the independent sample t test results revealed no significant differences between the two groups in terms of serum glucose and atherogenic indices at baseline (P>0.05). Levels of FBS and atherogenic indices did not change significantly in both groups at the end of the intervention. Moreover, results of ANCOVA test did not show statistically significant differences between the two groups in levels of

Table 2. Comparison of anthropometric measures and blood pressure in the L-carnitine group with the placebo group at baseline and after the intervention

Variable		L-carnitine group (n=23)	Placebo group (n=25)	Mean Difference (95%CI)	P**
Weight (kg)	Baseline	80.73±8.84	81.14±9.53	-0.40 (-5.62, 4.81)	0.877
	After 8 weeks	80.54±8.92	81.07±10.32	-0.11 (-1.11, 0.89)	0.827
	P*	0.567	0.846		
BMI (kg/m2)	Baseline	33.12±2.15	33.64±2.41	-0.51 (-1.81, 0.78)	0.431
	After 8 weeks	33.04±2.11	33.58±2.61	-0.03 (-0.46, 0.40)	0.873
	P*	0.559	0.719		
WC (cm)	Baseline	109.48±7.47	111.54±8.02	-2.05 (-6.45, 2.34)	0.352
	After 8 weeks	109.50±7.99	110.77±9.14	0.77 (-1.47, 3.02)	0.494
	P*	0.974	0.367		
HC (cm)	Baseline	115.15±6.19	114.93±7.76	0.22 (-3.79, 4.24)	0.911
	After 8 weeks	113.57±4.89	114.50±8.11	-1.13 (-2.49, 0.21)	0.098
	P*	0.013	0.296		
Waist-to-hip ratio	Baseline	0.95±0.04	0.97±0.06	-0.02 (-0.05, 0.01)	0.202
	After 8 weeks	0.96±0.04	0.96±0.07	0.01 (-0.01, 0.03)	0.257
	P*	0.110	0.669		
Waist-to-height ratio	Baseline	0.70±0.04	0.71±0.05	-0.01 (-0.04, 0.01)	0.222
	After 8 weeks	0.70±0.04	0.7±0.05	0.00 (-0.01, 0.02)	0.632
	P*	0.992	0.314		
Systolic blood pressure (mmHg)	Baseline	128.91±15.59	126.43±13.66	2.48 (-5.75, 10.72)	0.547
	After 8 weeks	125.00±11.18	129.82±12.65	-6.18 (-11.34, -1.01)	0.020
	P*	0.083	0.139		
Diastolic blood pressure (mmHg)	Baseline	83.26±8.99	81.42±9.51	1.83 (-3.41, 7.08)	0.486
	After 8 weeks	84.78±8.32	86.96±7.97	-2.86 (-7.09, 1.37)	0.181
	P*	0.382	0.008		

BMI, body mass index; WC, waist circumference; HC, hip circumference.

[a] Values are means ± SD.

P < 0.05 was considered significant.

[*] P values indicate comparison within groups (paired t-test).

[**] P values indicate comparison between groups (Independent sample t-test at baseline and ANCOVA test, adjusted for baseline values, after 8 weeks).

FBS and atherogenic indices at the end of the study, adjusted for baseline values and covariates (P>0.05).

Discussion

In the present study, L-carnitine supplementation did not lead to significant changes in anthropometric measures in obese women with knee OA after 8 weeks of intervention. There are limited studies with controversial results regarding effects of L-carnitine on anthropometric indices. Our findings are in line with some previous studies (14, 15, 26-30). Wutzke et al. (26) indicated that 3 g per day L-carnitine did not lead to significant changes in body weight in overweight subjects. In another study, Alshammari et al. (27) demonstrated that 8-week supplementation with L-carnitine (4 mg/kg) in obese women did not change body weight and

Table 3. Comparison of FBS and atherogenic indices in the L-carnitine group with the placebo group at baseline and after the intervention

Variable		L-carnitine group (n=23)	Placebo group (n=25)	Mean Difference (95%CI)	*P***
FBS (mg/dl)	Baseline	94.30±10.35	97.10±10.91	-2.80 (-8.83, 3.22)	0.355
	After 8 weeks	97.86±15.07	99.67±14.13	-0.04 (-6.27, 6.17)	0.988
	*P**	0.132	0.179		
VLDL (mg/dl)	Baseline	34.46±18.65	29.37±12.83	5.09 (-3.79, 13.97)	0.255
	After 8 weeks	35.19±15.72	29.23±13.88	3.19 (-3.14, 9.54)	0.315
	*P**	0.800	0.940		
Log (TG/HDL)	Baseline	0.47±0.27	0.43±0.23	0.03 (-0.11, 0.17)	0.634
	After 8 weeks	0.51±0.22	0.42±0.23	0.07 (-0.01, 0.15)	0.108
	*P**	0.324	0.725		
LDL-C/HDL-C	Baseline	2.46±0.64	2.54±0.65	-0.07 (-0.44, 0.28)	0.673
	After 8 weeks	2.36±0.63	2.59±0.97	-0.13 (-0.57, 0.31)	0.545
	*P**	0.380	0.794		
TC/HDL-C	Baseline	4.19±0.79	4.17±0.89	0.01 (-0.46, 0.49)	0.954
	After 8 weeks	4.09±0.74	4.20±1.14	-0.06 (-0.52, 0.39)	0.077
	*P**	0.535	0.851		

HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; VLDL , very low-density lipoprotein cholesterol. Values are means ± SD.

P < 0.05 was considered significant.

** P values indicate comparison within groups (paired t-test).*

*** P values indicate comparison between groups (Independent sample t-test at baseline and ANCOVA test, adjusted for baseline values, duration of OA, weight and calorie intake changes, after 8 weeks).*

BMI significantly compared with the placebo group. Furthermore, previous studies indicated that 2 g/day L-carnitine supplementation did not lead to significant changes in body weight and BMI in overweight and/or obese women after 8 weeks compared with baseline and the placebo group (26,27). Malaguarnera et al. (10) reported that L-carnitine supplementation (2 g/day for 24 weeks) in patients with non-alcoholic steatohepatitis did not change body weight and BMI significantly compared with baseline and the placebo group. Moreover, studies in type 2 diabetic patients showed that L-carnitine supplementation (2 g/day for 3 and 6 months, respectively) did not cause significant changes in body weight and BMI compared with baseline and the placebo group (14,30). However, Derosa et al. (31,32) reported that L-carnitine supplementation (2 g/day for 12 months) in combination with sibutramine and/or orlistat decreased body weight significantly in obese diabetic patients compared with the placebo group. These authors concluded that the observed effect may be due to the synergistic effects of sibutramine or orlistat and L-carnitine: the positive effect of L-carnitine on β-oxidation of fatty acids and its activity of the pyruvate dehydrogenase complex, and the anorectic properties of sibutramine and positive effects of orlistat on ingested dietary fat, gave a better improvement of these parameters compared to the drugs alone.

It is well recognized that abdominal obesity indices (WC and WtHR) are associated with cardiovascular risk factors, and those subjects with abdominal obesity usually carry physiologic profiles which places them at the high risk group of CVDs (33). Based on present study, L-carnitine supplementation did not lead to significant changes in WC, HC, and WtHR compared with the placebo group. Limited studies evaluated the effects of L-carnitine on abdominal obesity. In a study by Alipour et al. (28), L-carnitine supplementation resulted in significant decrease in WC, HC, and WtHR

in obese diabetic women compared with baseline; whilst no significant differences were observed between L-carnitine and placebo groups at the end of the study which was consistent with our study. Another study by Rafraf et al. (34) indicated that L-carnitine in combination with physical activity decreased WC and HC significantly in obese women compared with baseline and the placebo group; whilst it did not change WtHR significantly compared with baseline and the placebo group. In contrast to our study, Zhang et al. (35) reported that L-carnitine supplementation decreased WC and WtHR significantly in patients with metabolic syndrome compared with baseline and the placebo group. The diversity in findings may be due to differences in dosage and duration of intervention, background diseases, ethnicity and genotype.

Our study showed that L-carnitine decreased systolic blood pressure significantly compared with the placebo group; however it did not lead to significant changes in diastolic blood pressure compared with the placebo group. According to Zhang et al. (35) study, L-carnitine did not change blood pressure compared with baseline and the placebo group. Bloomer et al. (36) indicated that L-carnitine did not cause significant changes in blood pressure in prediabetic patients compared with baseline and the placebo group. Differences in baseline values, background disease and race/ethnicity can result in different findings.

Our results indicated no significant differences in atherogenic indices between the L-carnitine and placebo groups after supplementation. The lack of difference in atherogenic indices between the 2 groups might be due to the fact that participants' lipid profile was within the reference range, similar to the normal-weight participants. These results differ from other authors' findings in patients with type 2 diabetes (Malaguarnera et al., 2009) and patients with nonalcoholic steatohepatitis (Malaguarnera et al., 2010), in which the studied patients were hyperlipidemic. This inconsistency between results of different studies might be attributable to differences in baseline lipid profile status, background disease, and dosage and duration of L-carnitine administration. The limitations of the present study were a short period and low dose of the supplementation. In addition, we didn't measure serum L-carnitine level due to budget constraint. The strength of our study was weekly following-up by phone conversations.

In conclusion, L-carnitine did not lead to significant changes in cardiometabolic status in obese women with knee OA. Further studies with higher doses of L-carnitine are needed to explore its efficacy as an anti-obesity and anti-atherogenic agent in OA patients.

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