Health Scope. 2014 Winter; 3(1):e14615. DOI: 10.17795/jhealthscope-14615
Published online 2014 February 17. **Research Article**

Effect of L-Carnitine Supplementation on Metabolic Status in Obese Diabetic Women With Hypocaloric Diet

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Received: November 2, 2013; **Revised:** December 1, 2013; **Accepted:** December 10, 2013

Background: More than 500 million people worldwide are obese and around 320 million adults have type II diabetes, thus these two diseases are accounted as the fundamental health care problems. There is such a strong association between obesity and diabetes that the term diabesity is proposed for this connection. Since anti-obesity drugs have many side effects, experts have very few tools to fight obesity, while high doses of carnitine has no side effects compared to other drugs.
Objectives: The current study aimed to evaluate the effect of L-carnitine supplementation with low-calorie diet on the metabolic status in obese women with type II diabetes.
Patients and Methods: In this study, 60 obese premenopausal women with type II diabetes were randomly selected from the patients who referred to the Diabetes Clinic of Tabriz Red Crescent; they were 20 - 50 years old with a BMI greater than 30. The subjects were divided into two groups, case and control. Following the measurement of weight, waist circumference and recording personal information, weekly food intake program (based on a low calorie diet) was given to patients. For about 8 weeks, the case group received L-carnitine supplement (2 grams daily) combined with the low calorie diet, and the control group received placebo plus low-calorie diet. In this study, low calorie diet was defined as a regimen of 500 kcal lower than the patients required energy. Blood samples (5 mL of venous blood) were taken from all patients in the sitting position, and in fasting condition (for about 10 - 12 hours) between 7:00 AM and 9:00 AM. After separation of plasma by centrifugation for ten minutes in 3000 g, samples were analyzed to measure fasting blood glucose, lipid profile and insulin resistance.
Results: The results showed that L-carnitine supplement with low calorie diet reduced fasting blood glucose, triglycerides, cholesterol and LDL-C (Cholesterol, LDL-cholesterol) levels and decreased insulin resistance "HOMA-IR" ($P < 0.0001$), whereas in the control group, reduction of fasting blood glucose and triglycerides, cholesterol and LDL-C levels and decrease of insulin resistance "HOMA-IR" were lower than those of the case group ($P < 0.05$).
Conclusions: Due to the effect of L-carnitine supplementation (a dose of 1000 mg twice daily) with low-calorie diet on reduction of fasting blood glucose, triglycerides, cholesterol and LDL-C levels and insulin resistance (HOMA-IR), prescribing this supplement in obese patients with diabetes is recommended.

Keywords: Carnitine; Diabetes Mellitus; Insulin Resistance; Diet Therapy; Metabolic Syndrome X

1. Background

Prevalence of the global obesity is rapidly increasing among adults and adolescents due to high dietary fat intake. According to World Health Organization and the national institutes of health (NIH) classification, $25 < BMI < 29.9$ is defined as overweight, and $30 < BMI < 35$ is defined as obesity (1, 2). Diabetes mellitus is one of the serious human metabolic diseases, which causes disorders in lipid metabolism (3, 4). There are two types of diabetes. Type I diabetes is related to deficiency of insulin secretion, an auto-immune disease correlated with destruction of pancreatic β-cells (5). Type II, occurring in more than 90% of cases, is characterized by hyperglycemia, insulin resistance, and devastated insulin secretion (6). It is estimated that the prevalence of diabetes in patients is increasing dramatically from 2.8% to 4.4% in 2030 (7). It has been estimated that near 140 million people in the world are living with diabetes mellitus. Life expectancy may fall to half in developing countries by this disabling disorder, also appropriate treatment is often expensive or unavailable (8). The epidemic of obesity in the world is correlated with diabetes mellitus (9). Diabesity is a new term which refers to diabetes occurring in the context of obesity (10). Carnitine is a fatty acid oxidation facilitator which acts by interorganelle translocation of fatty acids (11). L-carnitine is a powerful aid due

Implication for health policy/practice/research/medical education:
As anti-obesity drugs have many side effects, experts have very few tools to fight obesity, while high doses of Carnitine has no side effects compared to other drugs. Therefore, the current study evaluated the effect of L-carnitine (2 g daily) with low-calorie diet in 60 obese postmenopausal women with type 2 diabetes (30 cases, and 30 controls).

to its role in the conversion of fat into energy (12, 13). L-carnitine is essential for beta-oxidation by transferring long-chain fatty acids from the cytosol to mitochondria. Lack of L-carnitine prevents using fat as a fuel (14).

L-carnitine is necessary for mitochondrial transport metabolism of long-chain fatty acids, thus for myocardial energetic metabolism. Fatty acids cross mitochondrial membranes as acylcarnitine derivatives to enter pathways for oxidation, acylation, chain shortening or chain elongation- desaturation. Therefore, L-carnitine-dependent fatty acid transfer is central to lipid metabolism; dietary supplementation of L-carnitine improves the utilization of fat providing marked reduction in plasma levels of TG (15). Despite the little information on the effect of oral administration of L-carnitine on human glucose homeostasis (16), some experimental studies indicated that the rate of glucose oxidation and L-carnitine concentration of plasma is low in patients with type II diabetes (17-21). Derosa et al. reported that L-carnitine significantly lowered the plasma lipoprotein (a) level in comparison with placebo in selected patients with hypercholesterolemia in newly diagnosed type II diabetes mellitus (22). Cuturic et al. reported that serum carnitine levels (acylcarnitine/free carnitine ratios) has a negative correlation with lipid levels, but positive correlation with fasting plasma glucose levels that is suggesting undesirable secondary effects of carnitine insufficiency resolved by carnitine supplementation (23).

2. Objectives

Given the varying results, the current study aimed to assess the effect of L-carnitine supplementation on glycemic and lipidemic profile in obese female patients with type II diabetes mellitus.

3. Patients and Materials

In this clinical trial, 60 obese premenopausal women with type II diabetes who referred to Diabetes Clinic of Tabriz Red Crescent during 6 months (2012 - 2013) aged 20 - 50 years old with a BMI > 30 who had not participated in any weight loss program in the last 6 months, and had no swing weight more than 1 kg were selected and randomly divided into two groups (30 patients in each group, case and control). After selection and primary checks, patients were evaluated for 8 weeks as case and control groups. Obesity in our study was defined as BMI > 30. The minimum sample size was calculated as 30 samples in each group (totally 60 cases) based on anthropometric index (adiposity). Exclusion criteria were liver disease, kidney cancer, pregnancy, lactation, menopause, insulin injections and use of any nutritional supplements as well as any other medications which affect balance of lipids as vitamin C or B6. The recommended amounts for using L-carnitine supplementation is 1 to 3 grams per day orally in divided doses (24). Intervention period was 8 weeks. Case group received L-carnitine supplement (2 grams twice daily in the morning and evening) with a low calorie diet. Control group received placebo with a low-calorie diet. Low calorie diet was defined as a regimen with 500 kcal lower than the patients required energy (required energy is calculated by the formula proposed by the food and nutrition board (FNB)). Dietary as daily intake units were instructed to the cases, and also a 7-day dietary were provided for them. From each of the subjects, 5 mL of venous blood samples was taken after 10 - 12 hours fasting before and after the intervention. After separation of plasma by centrifugation for ten minutes in 3000 g, samples were analyzed to measure fasting blood glucose, lipid profile and insulin resistance. Collected samples from the patients were evaluated by Pars Azmun kits (lot: 85001) and Abbott autoanalyzer (model Alcyon 300, made in France). LDL-C levels were calculated by Equation 1 (21).

Equation 1. $\mathrm{HOMA} = \frac{\mathrm{fastingserumglucose}\left(\frac{\mathrm{mg}}{\mathrm{dL}}\right)\mathrm{xfastingseruminsulin}\left(\frac{\mu\mathrm{U}}{\mathrm{mL}}\right)}{405}$

Insulin resistance was defined as the HOMA-IR index more than 3.99 calculated by Equation 2.

Equation 2. $\mathrm{LDL} - C = \mathrm{TotalCholestrol} - \left(\mathrm{HDL} - \mathrm{C} + \frac{\mathrm{TG}}{5}\right)$

The protocol of this study was approved by the ethics committee of Tabriz University of Medical Sciences and registered in Clinical Trial Registration System (at www.irct.ir) under the number IRCT138903164105N1. Obtained data are expressed as mean ± standard deviation, frequency and percentage. Data were analyzed by SPSS™ 17 software. Quantitative variables were compared by Student t-test. In all investigated cases, $P \leq 0.05$ was considered statistically significant.

4. Results

The demographic variables measured in the case and control groups to determine the compliance rate of participation were presented in Table 1. Anthropometric indices and body fat of all 60 cases were presented in Table 2.

Table 1. Demographic Variables Measured in Case and Control Groups Before Intervention

	Case [a], n = 30	Control [a], n = 30	P value
Age, y	37.03 ± 6.1	36.7 ± 5.6	0.76
Weight, kg	83.8 ± 8.21	84.23 ± 7.8	0.34
Height, cm	158.2 ± 7.5	157.6 ± 7.3	0.52
BMI [b], kg/m^2	33.4 ± 2.78	33.7 ± 2.81	0.91

[a] Data are presented as Mean ± SD.
[b] Abbreviation: BMI, body mass index.

Table 2. Obtained Results of Anthropometric Indices and Body Fat in Case and Control Groups Before and After Intervention [a]

Variable	Case, n = 30	Control, n = 30	P value [b]
Weight, kg			
Before	83.8 ± 8.21	84.23 ± 7.8	0.62
After	79.14 ± 7.65	81.56 ± 7.2	0.5
P value [c]	0.047 [d]	0.07	
BMI [e], kg/m [2]			
Before	33.4 ± 2.78	33.7 ± 2.81	0.91
After	31.62 ± 3.66	32.88 ± 2.7	0.87
P value [c]	0.43	0.5	
WC[e], cm			
Before	97.68 ± 9.25	98.22 ± 9.14	0.72
After	90.56 ± 8.91	93.78 ± 8.9	0.17
P value [c]	0.03 [d]	0.06	
HC [e], cm			
Before	118.06 ± 8.2	117.31 ± 7.7	0.93
After	111.86 ± 8.32	112.01 ± 7.5	0.69
P value [c]	< 0.0001 [d]	0.02 [d]	
WHR [e]			
Before	0.827 ± 0.07	0.837 ± 0.08	1
After	0.809 ± 0.08	0.838 ± 0.07	0.06
P value [c]	0.064	1	
BF [e]			
Before	41.12 ± 1.86	40.65 ± 1.81	0.86
After	36.51 ± 1.65	37.96 ± 1.76	0.91
P value [c]	0.046 [d]	0.053 [d]	

[a] Data are presented as Mean ± SD.
[b] Between groups analysis.
[c] Within groups analysis.
[d] Significant P values.
[e] Abbreviations: BF, body fat; BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-hip ratio.

The results of the experiments performed in the two groups before and after the intervention were presented in Table 3. As indicated in Table 2, patients in both the case and control groups had no significant difference before the intervention regarding weight, BMI, waist circumference, hip circumference, waist-hip ratio, and body fat. After the intervention reduction was seen in mentioned variables compared to their initial values in the both groups, but this reduction was statistically significant in the case group in weight, waist circumference, hip circumference, and body fat. Moreover, Table 3 indicates that the reduction in all measured variables (FBS, cholesterol, triglyceride, HDL-C, LDL-C, and HOMA-IR) was statistically significant in both case and control groups compared to their initial values, but the reduction in case group receiving L-carnitine supplement with low calorie diet was stronger, more prominent and remarkable than that of the control group (P value was < 0.0001 for all variables).

Table 3. Obtained Results on Fasting Blood Glucose, Insulin Resistance and Lipid Profile in Case and Control Groups Before and After Intervention [a]

Variable, mg/dL	Case, n = 30	Control, n = 30	P value [b]
FBS[c]			
Before	146.97 ± 20.45	157.47 ± 20.26	0.03 [e]
After	135.07 ± 16.14	149.1 ± 18.15	0.004 [e]
P value [d]	< 0.0001 [e]	0. 01 [e]	
Cholesterol			
Before	248.5 ± 33.26	244.2 ± 32.42	0.65
After	225.07 ± 32.19	233.57 ± 30.85	0.34
P value [d]	< 0.0001 [e]	0.01 [e]	
TG [c]			
Before	254.1 ± 30.9	249.73 ± 35.98	0.67
After	228.23 ± 27.25	234.87 ± 35.28	0.33
P value [d]	< 0.0001 [e]	0.01 [e]	
HDL-C [c]			
Before	38.97 ± 4.08	38.03 ± 4.18	0.39
After	43.23 ± 2.97	41.7 ± 3.52	0.07
P value [d]	< 0.0001 [e]	0.01 [e]	
LDL-C [c]			
Before	155.97 ± 23.38	153.13 ± 19.71	0.79
After	141.7 ± 17.94	145.1 ± 18.04	0.38
P value [d]	< 0.0001 [e]	0.013 [e]	
HOMA-IR [c]			
Before	4.18 ± 0.57	4.25 ± 0.55	0.76
After	3.3 ± 0.49	3.6 ± 0.48	0.01 [e]
P value [d]	< 0.0001 [e]	0.002 [e]	

[a] Data are presented as Mean ± SD.
[b] P value between groups analysis.
[c] Abbreviations: FBS, fasting blood sugar; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride.
[d] P value within groups analysis.
[e] Significant P values.

5. Discussion

It has been recognized that obesity is a disorder of energy balance, occurring when energy consumption and daily energy intake are not adequate. The present study demonstrated that 2 g/d oral L-carnitine supplementation in obese

women with type II diabetes mellitus was able to reduce body weight, adipose tissue accumulation as well as hyperglycemia and hyperinsulinaemia, therefore, the insulin resistant state was partially corrected by treatment. L-carnitine and its esters have been proposed as a treatment for many conditions such as heart failure, angina and weight loss due to their roles in reducing oxidative stress (25) and plasma inflammatory markers (26) that is consistent with our result. In our study, we observed a weight loss in both case and control groups, but this reduction was statistically significant in case group that received L-carnitine supplement compared to controls.

It has been reported that L-carnitine has a useful effect on several diabetic risk parameters, including plasma lipids and lipoprotein (27). This conversion could decrease triglycerides synthesis, and increase mitochondrial b-oxidation of fatty acids. Studies that support this opinion indicated that L-carnitine decreases serum cholesterol, triglycerides, and free fatty acids (28), the current study also observed a significant decrease in LDL-C, cholesterol and triglycerides in patients who received L-carnitine supplementation compared to the control group. Our results are consistent with those of Gonzalez-Ortiz et al. (29) and El-Metwally et al. (30) who reported that oral administration of L-carnitine improves dyslipidemia and decreases diabetic parameters. Reduction of serum hypertriglyceridemia in diabetic patients who consumed L-carnitine resulted in decrease of triglycerides synthesis in the liver or inhibition of triglyceride release from the liver. Moreover, L-carnitine induced significant reduction in total serum cholesterol in skeletal muscles of obese patients (31). These results are consistent with our results, we observed a significant reduction in both case and control groups, but the reduction was stronger and clinically valuable in the case group, which shows the role of L-carnitine supplementation in this regard.

Increased fat mobilization from adipose tissue and insulin resistance to the antilipolytic actions cause diminished muscular uptake of glucose and lead to hyperlipidemia. Disordered insulin action is related to an oversupply of lipids. Lipids increased availability causes elevated lipid stored in insulin target tissues (e.g. muscle, liver adipose) or increased plasma triglyceride (32). Gonzalez-Ortiz et al. in their study concluded that L-carnitine oral administration did not modify insulin sensitivity or the lipid profile. They administrated L-carnitine for a period of 4 weeks (29). However, in our study, oral administration of L-carnitine with low calorie diet for a period of 8 weeks modified lipid profile, and also reduced insulin resistance. In the current study, the weight loss due to oral administration of L-carnitine is associated with hypoglycemia because of elevated insulin sensitivity, thus decreasing insulin resistance in obese patients is due to regulating the cell energy metabolism or reducing free fatty acids. These results are in agreement with those of Gonzalez-Ortiz et al. (29) studies.

In addition, enhanced secretion of insulin from the beta-cells of the pancreatic islets or among an extra pancreatic mechanism is probably mediating hypoglycemia induced by L-carnitine. Moreover, the inflammatory effect of cytokine release during diabetes is one of the causative agents for the insulin resistance; L-carnitine may reduce this effect of cytokines (33). Based on the results of different studies, intestinal L-carnitine absorption is saturated within two grams, so the oral administration of L-carnitine more than 2 grams per meal, is not beneficial and not recommended. It seems that L-carnitine supplementation before each meal has a good effect in its absorption (34). Receiving 15 grams of L-carnitine orally per day has no side effects in healthy persons (OSL, observed safe level). The National Institutes of Health (NIH) has noted that L-carnitine supplementation is well tolerated by most individuals in the intervention up to six months. However, there is the possibility of side effects such as gastrointestinal disorders including nausea, vomiting, stomachache, mild diarrhea, and also in a small number of cases who received this supplement, changes in body odor as fishy smell or euphoric mode was reported (35, 36). Due to the effect of L-carnitine supplementation (a dose of 1000 mg twice daily) with low-calorie diet on reducing fasting blood glucose, triglycerides, cholesterol and LDL-C levels, and insulin resistance (HOMA-IR), prescribing this supplement in obese diabetic patients is recommended. Last but not least, there are some limitations to the study including lack of possibility to examine other indicators of oxidative stress and antioxidant system components such as oxidized LDL-C, MDA, enzymatic activity of SOD and GPx, lack of patient cooperation for long-term follow-up like 6 months, one year and financial constraints in the evaluation of various serum inflammatory markers such as IL-10 and TNF-α.

Acknowledgements

The authors wish to thank all patients and their families for their support and involvement in this study. This article was extracted from the result of PhD degree in Nutritional Sciences thesis with registration number of 34 in Tabriz University of Medical Sciences.

Authors' Contribution

A, study design; B, data collection; C, statistical analysis; D, data interpretation; E, manuscript preparation; F, literature search; G, fund collection. Baitullah Alipour (A, B, E), Ali Barzegar, (A, B, E, F), Farid Panahi (D, E, F), Abdolrasol Safaeian (C) and Masoud Es. haghi (F).

Financial Disclosure

The authors declare that there are no conflicts of interest.

Funding/Support

This study was supported by Research and Technology Deputy, Tabriz University of Medical Sciences.

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