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Research Article

Effects of Oral L-carnitine Supplementation on Visceral Proteins, C-reactive Protein, Homocysteine and Blood Lipid of Hemodialysis Patients: A Randomized Clinical Trial

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Abstract

Background and Objective: Protein-energy malnutrition and carnitine deficiency are common in hemodialysis patients. Carnitine supplementation may improve the general health and quality of hemodialysis patients' lives. The aim of study was to determine the effects of L-carnitine supplementation on the visceral protein status, malnutrition status and blood lipid profile in hemodialysis patients. **Materials and Methods:** This study was a randomized clinical controlled trial by participating of 42 Hemodialysis patients. Participants were randomly divided into 2 groups, the carnitine group (CAG) consumed oral syrup of L-carnitine containing 1000 mg of carnitine per day for 12 weeks but the control group (COG) did not use any carnitine. Serum levels of albumin, pre-albumin, transferrin, total lymphocyte count (TLC), C-reactive protein (CRP), homocysteine and lipid profiles were measured from the baseline and at the end of the study. The malnutrition-inflammation score (MIS) was used to assess the nutritional status of patients. **Results:** The variations and mean concentration of all variables except LDLc were not statistically significant. The mean difference of LDLc concentration in CAG and COG were -4.3±38.3 and 26.7±55.4 mg dL^{-1}, respectively ($p = 0.05$). Based on the MIS, 52.9% of patients in CAG and 36% of COG had moderate degree of malnutrition at the baseline. **Conclusion:** A daily supplementation of 1000 mg of L-carnitine for three months did not affect the improvement of serum albumin, pre-albumin, transferrin, TLC, CRP, homocysteine, triglyceride, total cholesterol and BMI of hemodialysis patient but it may prevent lipid disorders and cardiovascular disease in these patients by reducing serum LDLc.

Key words: Hemodialysis patients, l-carnitine, c-reactive protein (CRP), malnutrition-inflammation score (MIS), blood lipids

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

More than one million people die annually due to the growing the end stage renal diseases (ESRD) in the worldwide[1-3]. In Iran, the incidence of ESRD has increased from 49.9-64 per million population in a 6 years period (2000-2006)[4] and about 52.7% of these patients were treated with hemodialysis[4] that increased 15% annually[5].

Despite achieving technological advances in the ambit of dialysis and adequate protein intake, long-term dialysis leads to malnutrition. Among the potential causes of malnutrition, inadequate energy intake and micro-nutrients deficiency were observed in these patients. Diet restrictions, loss of appetite, loss of water soluble nutrients during hemodialysis and high production of inflammatory cytokines due to a poor nutrition status in these patients[6,7].

The protein-energy malnutrition is common in hemodialysis patients[7] so that the prevalence of malnutrition in hemodialysis patients[8] is 23-76%. Two types of malnutrition in these patients are reported, the first type is characterized by low food intake, loss of lean body mass and normal serum albumin level and the second one is characterized by inflammation, atherosclerosis, low serum albumin level and normal food intake[9]. Malnutrition and inflammation often leads to malnutrition-inflammation syndrome and malnutrition-inflammation atherosclerosis, the important cause of mortality in this disease[10]. Malnutrition is a common complication in dialysis patients, about 40% of patients receive insufficient protein and energy and 10% of patients suffering from severe malnutrition[11].

There is a strong relationship between nutritional factors and systemic inflammation factors and dialysis complications[12-14]. In patients on dialysis, inflammatory reactions release inflammatory mediators such as interleukin-1, interleukin-6 and tumor necrosis factor alpha (TNFa), lead to synthesis of CRP, decreased serum albumin and prealbumin level and increased homocysteine and endothelin types 1 that these changes can lead to progression of atherosclerosis in patients with ESRD[3,14-17].

Proinflammatory cytokines caused malnutrition by increasing protein catabolism. L-carnitine suppresses the inflammatory response and increases the anabolic processes[18]. The inflammation in these patients can cause several complications including malnutrition, anemia, atherosclerosis and cardiovascular disease, so in patients treated by dialysis, the prevention of the systemic inflammatory processes and treatment of malnutrition can reduce morbidity and mortality in these patients remarkably[3,15,16,19].

According to previous studies, acute phase proteins disorder such as low serum albumin level, high CRP and homocysteine level are common in hemodialysis patients[16,20,21]. Low serum albumin has been associated with increased mortality, so that a reduction of 1 mg dL^{-1} serum albumin level has been associated with increasing 47% mortality in hemodialysis patients and 38% of peritoneal dialysis patients[14].

L-carnitine (L-3-hydroxi-4-N-trimethylammonio-butanoate), an essential hydrosoluble molecule for human, is involved in many metabolic processes, such as ketogenesis mitochondrial energy compliance and long-chain fatty acids transference across the inner mitochondrial membrane and controls the rates of long-chain fatty acids beta oxidation so it is a pivotal molecule in human energy metabolism system[22]. Carnitine deficiency (free carnitine <40 μmol L^{-1}) is common in long-term dialysis and is observed in half of female patients and one-third of male patients with ESRD[20]. Serum free Carnitine levels in patients with ESRD who don't dialyze is higher than hemodialysis patients. In long-term dialysis patients, carnitine synthesis is reduced and is lost during hemodialysis so Level of serum free carnitine during hemodialysis drops so that the serum levels reduction in each session[23] is 75%.

The L-carnitine supplementation reduces proinflammatory cytokines production and improves protein synthesis, nitrogen balance and nutritional status in dialysis patients[24]. Some studies showed that L-carnitine supplementation can improved serum albumin levels[24-28]. Normal serum albumin levels can reduce the levels of CRP, transferrin, hemoglobin and need for erythropoietin[29] and increased body mass index[28]. In most cases, L-carnitine supplementation improves the general health and quality of life in hemodialysis patients, however there are various studies with negative results for L-carnitine supplementation in ESRD[30]. This study was designed and implemented to investigate the effects of oral L-carnitine supplementation on malnutrition status, visceral proteins level, blood lipid profile and anthropometric status of hemodialysis patients.

MATERIALS AND METHODS

Study type and participants: The present study was a randomized controlled clinical trial performed with the participation of patients on ceaseless dialysis in hemodialysis centers of Seyed-al-Shohada, shahid Rahnamoun and shahid Sadooghi hospitals in Yazd from September, 2013 to June, 2014. Participants older than 20 years on ceaseless dialysis

treatment for at least 1 year could participate in this intervention study. Having an infectious, liver or cancer diseases, consuming L-carnitine for at least 8 weeks prior to the start of the study, consuming corticosteroids, having a kidney transplantation or participating in another research project made up the exclusion criteria.

Sample size and designing: Considering a study potency of 80%, $\alpha = 0.05$, an attrition of 10% during the study and previous studies parameters[31], the final sample size was determined to be 50 patients. They were divided by random number table into 2 groups, carnitine (CAG) and control group (COG). Patients in the CAG took 1000 mg oral supplementation of L-carnitine in the form of 20 mL L-carnitine syrup made by the Alborzdarou Company (Alborzdarou Co, Tehran, Iran) every day after dinner for 12 weeks. However, patients in the COG did not receive any L-carnitine supplementation. All patients were undergoing hemodialysis 2-3 times per week for 4 h by Hemofane and Polysulfone filters and only 2 patients were on hemodialysis once per week. Patients were visited monthly in dialysis centers and the supplements were delivered to them gradually and in order to be certain of syrup consumption, the completed drug recall forms were taken from patients.

Measurements: Demographic characteristics including age, gender, weight, height, body mass index (BMI), dialysis duration and diseases were recorded from the baseline. Patients wearing minimal clothing were weighed at baseline and at the end of the study after hemodialysis using a Seca digital scale made in Germany, with an accuracy of 100 g. Their height with bare feet was measured using a stadiometer with an accuracy of 0.05 cm. Participants were asked not to change their physical activity, diet, medication and lifestyle during 3 months. Dietary intakes were assessed using a 24 h dietary recall (24HR) for 3 consecutive days from the baseline and at the end of study.

Patients' nutritional status were assessed at the beginning of the study using the malnutrition-inflammation score (MIS) method. The MIS forms were completed by a nutritionist and a physician for each patient. The MIS form included 10 components. The first part was about the patient's related medical history and included the changes in dry weight, dietary intake, gastrointestinal symptoms, functional capacity, co-morbidity including number of years on dialysis. The second part concerned the subject's physical exam (according to SGA criteria) and included decreased subcutaneous fat and signs of muscle wasting. This form also included three other components: BMI, serum albumin and serum TIBC (Total Iron Binding Capacity). Each component is scored among 0-3, final score is used to determine the malnutrition rate. Normal nutritional status is shown by 0-7, moderate and severe malnutrition is demonstrated by 8-18 and 19-30 points[32].

The physical activity levels were determined by asking from patients and their companions. Patients who were affiliated with someone else on a personal works such as going to bath, were categorized as "very light", patients who done their own personal works, were categorized as "light" and individuals who done outside work in addition to their own personal work were categorized as "moderate ".

All biochemical tests were done at the DAY Medical Specialized Laboratory in the Yazd city. About 10 mL of venous blood was taken by a hemodialysis department nurse before hemodialysis from the baseline and the end of the study. Samples were immediately transferred to an ice flask and then sent to the laboratory less than 30 min after being drawn. For serum separation, samples were centrifuged at room temperature up to 1500 rpm. After centrifugation, the TLC analysis was done and the rest samples were removed and frozen completely at -80°C. The samples of the first and second stages were tested simultaneously in a single day. Serum CRP concentration was measured using latex immunoturbidimetric (LIA) method. Serum homocysteine and transferrin concentration were measured enzymatic, albumin concentration was measured by colorimetric method and prealbumin concentration was evaluated using Biosystem kit (production of Spain). Patients' TIBC levels were measured at the beginning of the study to assess patients' nutritional status.

Statistical analysis: Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 16.0 and 24 h data was analyzed using the Nutritionist 4 (N4) software. The chi-square test was used to compare qualitative variables between the two groups. Because all quantitative parameters had normal distribution according to the Kolmogorov-Smirnov test, the student t-test and the paired t-test were used to compare parameters between and within groups, respectively. Results are expressed as Mean±SD and differences are considered significant at $p \leq 0.05$.

Ethical considerations: According to the inclusion and exclusion criteria, supplementation in the present study was safe and completely ethical. At baseline, the goals and methods of the study were explained to patients and an informed consent form was signed by each participants. The

patients could withdraw at any time or at any stage of the research. This study was approved by the Shahid Sadoughi University of Medical Sciences Ethical Committee and was registered at www.irct.ir with the code of IRCT2013070913 160N2.

RESULTS

Out of the 50 hemodialysis patients that were enrolled at the beginning of the study, 1 subject due to unwillingness, 3 subjects due to non-compliance, 2 subjects due to death and 2 subjects due to kidney transplantation were excluded. About 42 patients completed the study (Fig. 1). The demographic characteristics of patients in both groups at the beginning of the study were reported in Table 1. As it can be seen, the patients in the COG were not significantly different with CAG in terms of average age, duration of dialysis, gender, weight and BMI. In terms of underlying diseases like diabetes, hypertension or dyslipidemia, there was no significant difference between the 2 groups.

According to 24 h, energy and macronutrients intake were not different significantly between and within 2 groups before and after the intervention (Table 2). Insignificant MIS values between the two groups at the beginning of the study showed an appropriate distribution of subjects in terms of nutritional status in 2 groups. It can be concluded that the average degree of malnutrition did not interfere with this study (Table 3). The MIS values showed that 52.9% of patients in CAG and 36% of patients in COG suffered from average degree of malnutrition-inflammation.

The mean of weight, BMI, serum albumin, pre-albumin, transferrin, TLC, homocysteine, CRP, LDL, triglycerides and total cholesterol before and after the study was reported in Table 4. The mean BMI was reduced after 3 months in the COG but this difference was not significant compared to the CAG. The mean of serum albumin levels was different significantly in COG at the end of the study but this difference was not clinically significant. At the end of study the mean of serum albumin levels decreased but this change was not significant between the 2 groups.

After the study the prealbumin levels were decreased in the CAG and increased in the COG but this finding was not statistically significant. The serum pre-albumin levels were not different between the two groups ($p = 0.3$). In both groups the mean transferrin levels were increased after the intervention but this difference was not significant between the two groups ($p = 0.56$).

At the end of the study the differences of serum TLC, TG and total cholesterol between the two groups were not significant. The mean serum homocysteine levels were different significantly before and after the study in the COG ($p = 0.009$). In addition, homocysteine levels decreased in both groups after the study but this difference was not significant between the two groups ($p = 0.8$). At the end of the study, the mean serum LDL levels were different significantly in COG ($p = 0.02$), it decreased in the CAG but increased in the COG. The p-value for this difference between the two groups before and after the study was $p = 0.05$.

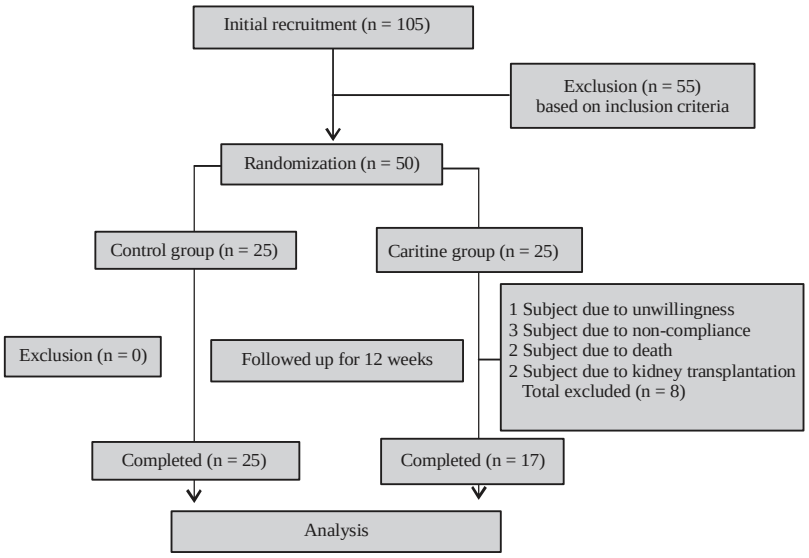

Fig.1: Image of implementation study

Table 1: Comparison of patients' characteristics of the two groups at the beginning of the study

Quantitative variables	Carnitine group	Control group	p-value*
Age (year)	63.40±12.9	62.10±10.2	0.72
Weight (kg)	66.68±14.0	65.90±11.5	0.84
BMI (kg m^{-2})	24.40±3.40	24.60±3.0	0.82
Duration of dialysis (year)	3.47±2.35	3.35±1.90	0.86
Qualitative variables	N (%)	N (%)	p-value**
Sex			
Female	4.00 (23.5)	9.00 (36)	0.4
Male	13.00 (76.5)	16.00 (64)	0.5
Diabetes	12.00 (70.6)	15.00 (60)	0.5
Hypertension	10.00 (58.8)	17.00 (68)	0.5
Dyslipidemias	1.00 (5.9)	3.00 (12)	
Physical activity level		0.90	
Very light	4.00 (23.5)	7.00 (28)	
Light	18.00 (47.1)	11.00 (44)	
Moderate	7.00 (28.0)	5.00 (29.4)	

*Student t-test, **Chi square test

Table 2: Comparison of patient dietary intake of the two groups at the beginning and at the end of the study

Characteristics	Before	After	p-value*
Energy (kcal/day)			
Carnitine group	1189±258	1234±514	0.43
Control group	1210±595	1101±335	0.73
**p-value	0.7	0.83	
Protein (g/day)			
Carnitine group	41.0±13.6	44.0±17.0	0.32
Control group	41.0±22.0	39.0±13.0	0.78
p-value	0.54	0.92	
Carbohydrate (g/day)			
Carnitine group	201.3±38.0	209.0±82.0	0.24
Control group	204.0±112.0	184.0±60.0	0.53
p-value	0.45	0.65	
Fat (g/day)			
Carnitine group	23.5±6.0	28.0±9.5	0.94
Control group	24.0±18.0	21.0±4.2	0.86
p-value	0.29	0.65	

*Paired t-test, **Student t-test

Table 3: Comparison of patient malnutrition-inflammation status of the two groups at the beginning of the study using MIS

Characteristics	Carnitine group	Control group	p-value
MIS score	7.00±2.96	6.96±2.57	0.96*
MIS status	N (%)	N (%)	
Normal	8 (47.1)	16 (64)	0.22**
Intermediate	9 (52.9)	9 (36)	
Severe	0	0	

*Student t-test, **Chi-square test

DISCUSSION

Present study showed that a daily supplementation of 1000 mg of oral syrup L-carnitine for 12 weeks did not affect the serum visceral proteins levels, CRP, homocysteine, triglycerides, total cholesterol, weight or BMI of hemodialysis patients and it is only possible to prevented lipid disorders and cardiovascular disease by reducing LDL cholesterol in these patients. At the beginning of the study, the demographic, clinical and lifestyle features that could affect the malnutrition status included age, sex, marital status, educational level, daily dietary intake, anthropometric factors, blood pressure, physical activity level, history of any disease, weight loss, drug use and dietary supplementation were examined. The mean of age, weight, sex, BMI, history of diabetes, dyslipidemia and hypertension, food usage and drug supplements, duration of onset of dialysis and the frequency of dialysis per week were not different significantly between both groups, which indicated appropriate random distribution between the groups. At the beginning and at the end of the study the mean of energy, carbohydrate, protein and fat intake in the both groups were not different significantly.

Table 4: Outcome measures in study participants

Characteristics	Before	After	p-value	Change
Weight (kg)				
Carnitine group	66.7±13.9	66.7±13.4	0.9	0.04±1.54
Control group	65.8±11.5	65.4±11.9	0.4	-0.48±2.54
**p-value	0.8	0.73		0.45
BMI (kg m^{-2})				
Carnitine group	24.4±3.4	24.4±3.3	0.86	0.02±0.54
Control group	24.6±3.0	24.4±3.2	0.31	-0.20±0.92
p-value	0.8	0.99		0.4
Albumin (mg dL^{-1})				
Carnitine group	3.77±0.32	3.69±0.4	0.22	-0.08±0.26
Control group	3.87±0.38	3.61±0.4	0.004	-0.26±0.41
p-value	0.4	0.5		0.12
Prealbumin (mg dL^{-1})				
Carnitine group	109.1±31.7	106.1±27.0	0.76	-3.02±40.94
Control group	105.0±30.7	115.5±31.3	0.21	10.50±41.00
P-value	0.7	0.3		0.3
Transferrin (mg dL^{-1})				
Carnitine group	272.0±93.4	272.6±75.0	0.98	0.6±136.6
Control group	272.0±65.6	293.2±72.5	0.28	21.4±95.84
p-value	0.9	0.4		0.56
Total lymphocyte count (mg dL^{-1})				
carnitine group	25.3±8.6	26.4±10.50	0.63	1.08±9.20
Control group	23.6±7.3	23.64±7.65	0.81	0.40±8.34
p-value	0.5	0.3		0.8
Homocysteine (mg dL^{-1})				
Carnitine group	31.5±8.7	26.4±8.8	0.13	-5.2±13.5
Control group	31.9±7.1	25.8±6.4	0.009	-6.2±10.9
p-value	0.9	0.8		0.8
C-reactive protein (µg L^{-1})				
Carnitine group	7.2±8.5	9.1±11.5	0.4	1.95±9.4
Control group	4.9±8.2	5.5±8.1	0.8	0.60±10.8
p-value	0.4	0.2		0.7
Low density lipoprotein (mg dL^{-1})				
Carnitine group	93.8±26.4	89.5±29.7	0.60	-4.3±38.2
Control group	77.8±36.2	104.4±36.6	0.02	26.7±55.4
p-value	0.12	0.17		0.05
Triglyceride (mg dL^{-1})				
Carnitine group	129.4±54.6	136.4±78.3	0.56	6.94±48.4
Control group	110.8±76.9	119.0±80	0.54	8.20±66.45
p-value	0.4	0.5		0.9
Total cholesterol (mg dL^{-1})				
Carnitine group	167.1±36.0	168.8±45.8	0.89	1.70±48.3
Control group	145.5±45.9	146.5±0.05	0.86	1.08±30.1
p-value	0.11	0.1		0.9

*Paired t-test, **Independent t-test

Present study evaluated the MIS score and dietary intake for each person at the beginning of the study and the MIS score was not different significantly between the two groups, therefore it showed the mean of malnutrition degree in the groups did not interfere in the study.

The current study showed that the carnitine supplementation had no significant effect on serum albumin level. The mean of serum albumin levels were not different by the 1 g intravenous L-carnitine supplementation in hemodialysis patients in Suchitra *et al.*[32] study. Shakeri *et al.*[27] and Mortazavi *et al.*[31] also showed that the consumption of oral l-carnitine with dosage of 1000 and 750 mg did not alter significantly the serum albumin level in hemodialysis patients. Present study also showed that the mean of serum albumin decreased significantly in COG at the end of the study but this difference was not clinically meaningful and this

decreased was not significant in the CAG. Chazot *et al.*[28] showed that administration of 15 mg kg^{-1} intravenous carnitine in hemodialysis patients was reduced the mean serum albumin levels significantly while didn't have any significant change on other anthropometric and nutritional factors. The studies of Argani[26] and Trovato[24] on hemodialysis patients and Mortazavi *et al.*[18] study on peritoneal dialysis patients showed that taking 500-1000 mg of oral l-carnitine can improve serum albumin. Vesela *et al.*[33] in a study on 12 hemodialysis patients showed that injection of 15 mg kg^{-1} of carnitine for 6 months increases serum albumin in these patients. D uranay *et al.*[2] and Savica *et al.*[3] showed that administration of 20 mg kg^{-1} of intravenous carnitine after each hemodialysis session for 6 months elevated serum albumin. Yang *et al.*[34] showed that the oral and intravenous carnitine supplementation does not show a significant change in serum albumin and CRP levels. Duranay *et al.*[2] and Savica *et al.*[3] showed that 20 mg kg^{-1} body weight carnitine injections after each dialysis session reduced serum CRP levels significantly. Yang[34] showed that carnitine consumption in hemodialysis patients had no effects on serum CRP and in current study, no significant difference was observed in serum CRP levels between the two groups.

This study showed that the 1 g oral l-carnitine supplementation for 12 weeks did not change significantly the serum pre-albumin levels in hemodialysis patients and also, the increase in the mean of total lymphocyte count (TLC) was not significant in the CAG. In the scope of present study, a similar study that evaluated the effect of carnitine on these two nutritional indices has not been done so far.

Santo Signorelli[17] showed that 600 mg intravenous prppionil l-carnitine three times a week for 1 year decrease the mean homocysteine levels significantly in hemodialysis patients however, this was observed in placebo group. Mortazavi[18] found that 750 mg oral l-carnitine supplementation for 9 months increase the mean homocysteine levels significantly in peritoneal dialysis patients (levels of homocysteine in the group of carnitine from 21.4±8/08 -25/7±6.85, $p = 0.019$) however that was not significant in placebo group but we observe no significant change in the mean homocysteine levels.

Elisaf *et al.*[35], Kosan *et al.*[36] and Mortazavi *et al.*[18] showed that the use of intravenous or oral carnitine did not alter the serum levels of cholesterol and triglyceride in hemodialysis patients, While Argani *et al.*[26] and Naini *et al.*[37] showed that the oral intake of l-carnitine was associated with a decrease in triglyceride levels in hemodialysis patients. Shakeri *et al.*[27] showed that 1 g oral l-carnitine supplementation decreases the mean of serum triglyceride and cholesterol levels significantly in hemodialysis patients, which differed from the results of the meta-analysis[34] and this meta-analysis showed that administration of carnitine in these patients had no effects on the total cholesterol and triglyceride levels as well as our study.

The studies on the effect of carnitine on serum LDL in hemodialysis patients are limited. Kosan *et al.*[36], Shakeri[27] and Naini *et al.*[37] did not show significant changes in serum LDL levels after carnitine consumption in hemodialysis patients, however Mortazavi[18] in a study on peritoneal dialysis patients showed that taking 750 mg oral carnitine per day can lower the serum LDL levels. Our study showed that was not significantly changed the serum LDL. However, the absence of carnitine supplementation in the COG was associated with a significant increase in LDL levels and these changes between the groups was statistically significant ($p = 0.05$). In this study we assumed that carnitine deficiency is common in hemodialysis patients, so at the beginning of the study the serum carnitine levels were not measured and this is our study limitation. It is suggested that a large study with different large doses of L-carnitine be conducted.

CONCLUSION

This study showed that a daily supplementation of 1000 mg of oral syrup L-carnitine for 12 weeks did not affect the serum visceral proteins levels, CRP, homocysteine, triglycerides and total cholesterol, weight or BMI of hemodialysis patients and it is only possible to prevented lipid disorders and cardiovascular disease by reducing LDL cholesterol in these patients.

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