Nutrition 31 (2015) 475–479

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Antiinflammatory effects of L-carnitine supplementation (1000 mg/d) in coronary artery disease patients

Bor-Jen Lee M.D., Ph.D. [a], Jun-Shuo Lin M.S. [b], Yi-Chin Lin Ph.D. [b,c], Ping-Ting Lin Ph.D. [b,c,*]

[a] The Intensive Care Unit, Taichung Veterans General Hospital, Taichung, Taiwan
[b] School of Nutrition, Chung Shan Medical University, Taichung, Taiwan
[c] Department of Nutrition, Chung Shan Medical University Hospital, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 6 June 2014
Accepted 5 October 2014

Keywords:
L-carnitine
Inflammation
Antioxidant
Supplement
Coronary artery disease

ABSTRACT

Objective: Inflammation mediators have been recognized as risk factors for the pathogenesis of coronary artery disease (CAD). The purpose of this study was to investigate the effect of L-carnitine supplementation (LC, 1000 mg/d) on inflammation markers in patients with CAD.
Methods: We enrolled 47 patients with CAD in the study. The patients with CAD were identified by cardiac catheterization as having <50% stenosis of one major coronary artery. The patients were randomly assigned to the placebo (n = 24) and LC (n = 23) groups and the intervention was administered for 12 wk. The levels of LC, antioxidant status (malondialdehyde and antioxidant enzymes activities), and inflammation markers (C-reactive protein [CRP], interleukin [IL]-6, and tumor necrosis factor [TNF]-α) were measured.
Results: Thirty-nine participants completed the study (19 placebo; 20 LC). After LC supplementation, the levels of inflammation markers were significantly reduced compared with the baseline (CRP, $P < 0.01$; IL-6, $P = 0.03$; TNF-α, $P = 0.07$) and those in the placebo group (CRP, $P < 0.05$; IL-6, $P = 0.04$; TNF-α, $P = 0.03$). The levels of inflammation markers were significantly negatively correlated with the levels of LC and antioxidant enzymes activities ($P < 0.05$).
Conclusions: We suggest that LC supplementation, due to its antioxidant effects, may have potential utility to reduce inflammation in CAD.

Introduction

Inflammation and atherosclerosis have become well established over the past decade. Many theories describing the atherosclerotic disease process are correlated with inflammation status [1,2]. Mounting evidence indicates that a higher inflammation status plays a key role in development of coronary artery disease (CAD) [1,2]. In clinical studies, the levels of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α were commonly used as inflammation markers to predict the risk for CAD [3–5]. In the inflammatory cascade of atherosclerosis, the proinflammatory risk factors such as oxidized low-density lipoproteins and proinflammatory cytokines (e.g., TNF-α) may induce IL-6 secretion. IL-6 is a messenger cytokine that is secreted by macrophages and smooth muscle cells in the atherosclerotic lesion. Then, CRP is released as a product of hepatic stimulation and inflammation, under the regulation of IL-6. Finally, systemic inflammation is triggered and results in elevated levels of inflammation markers attributed to atherosclerosis [4].

L-carnitine (β-hydroxy-γ-trimethyl-amino-butyric acid; LC) is an essential compound that is synthesized from lysine and methionine [6]. LC assists in the β-oxidation of long-chain fatty acids and transports fatty acids into the mitochondrial matrix [6,7]. Recently, an in vitro study demonstrated that LC plays a critical role in inflammatory diseases by modulating inflammatory cell functions [8]. LC might have the potential to control inflammation by reduction of major inflammatory cytokines,

This study was supported by a grant from the Chung Shan Medical University (CSMU-INT-101-09), Taiwan. BJL carried out the study, performed the data analyses, and drafted the manuscript. JSL and YCL carried out the study and sample analyses. PTL conceived the study, participated in its design, and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript. The authors have no conflicts of interest to declare.

* Corresponding author. Tel.: +886 424730022; fax: +886 423248175.
E-mail address: apt810@csmu.edu.tw (P.-T. Lin).

http://dx.doi.org/10.1016/j.nut.2014.10.001
0899-9007/

including nuclear factor-kappa B (NF-κB) and TNF-α [8,9]. Most clinical trials have examined antiinflammatory effect of LC supplementation at doses of 1000 to 1200 mg/d in the patients on hemodialysis [10–13], but not all of them have shown an effect on inflammation markers [13]. To our knowledge, there is no published information about the antiinflammatory effect of LC supplementation in patients with CAD. The Ministry of Health and Welfare in Taiwan recommends a daily dietary intake of ≤2000 mg of LC. It is worthwhile to investigate whether LC supplement shows an antiinflammatory effect in patients with CAD. Thus, we tested a dose of 1000 mg/d in patients with CAD and examined whether this dose could be a dietary supplement for daily use. The purpose of this study was to investigate the effect of LC supplements (1000 mg/d) on inflammation markers in patients with CAD.

Materials and methods

Participants

This study was designed as a single-blinded, randomized, parallel, placebo-controlled study. Patients with CAD were recruited from the cardiology clinic of Taichung Veterans General Hospital, which is a teaching hospital in central Taiwan. CAD was identified by cardiac catheterization as having <50% stenosis of one major coronary artery or receiving percutaneous transluminal coronary angioplasty. Patients with diabetes, liver, or renal diseases were excluded to minimize the influence of other cardiovascular risk factors. Patients undergoing statin therapy or currently using vitamin supplements were also excluded. Informed consent was obtained from each participant. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taiwan and registered at ClinicalTrials.gov (NCT01819701).

With a sample size calculation, we expected that the change in the levels of antioxidant enzymes activities would be 5.0 ± 7.0 U/mg of protein after LC supplementation; therefore, the desired power was set at 0.8 to detect a true fact and at an α value = 0.05 with a minimum sample size of 18 in each intervention group. We enrolled 47 patients with CAD in this study and randomly assigned them to the placebo (n = 24) or LC (n = 23) group. The LC and placebo (starch) capsules were commercially available preparations (New Health Taiwan Co., Ltd.). The intervention was administered for 12 wk. The participants were instructed to take two capsules (500 mg) daily, equal to 1000 mg/d. To monitor compliance, the researchers reminded participants to check the capsule bag every 4 wk to confirm that it was empty, and we measured the serum LC level before and after intervention. Participants' age, blood pressure, smoking, drinking, and exercise habits were recorded. Body weight, height, and waist circumferences were measured and the body mass index (kg/m^2) was calculated.

Blood collection and biochemical measurements

Fasting venous blood samples (15 mL) were obtained to estimate the hematologic and vitamin status. Blood specimens were collected in Vacutainer tubes (Becton Dickinson, Rutherford, NJ, USA) that contained EDTA as an anticoagulant or that contained no anticoagulant as required. Serum and plasma were prepared after centrifugation (3000*g*, 4°C, 15 min) and were then stored at −80°C until analysis. Hematologic parameters (serum creatinine, total cholesterol, triacylglycerol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol) were measured by an automated biochemical analyzer (Hitachi-7180 E, Tokyo, Japan). Plasma malondialdehyde (MDA) was determined using the thiobarbituric acid reactive substances method, as previously described [14]. Serum was diluted with 400 × sample diluent for LC measurement. Serum level of LC was measured by enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (Cusabio, Wuhan, China) according to the supplier's instructions and the detection range for the analysis of LC were 0.8 to 50 μmol/L. The intra- and inter-assay precision were <8% and <10%, respectively.

Serum level of CRP was quantified by particle-enhanced immunonephelometry with an image analyzer (Dade Behring, Deerfield, IL, USA). Serum levels of IL-6 (eBioscience, San Diego, CA, USA) and TNF-α (R&D Systems Inc., McKinley Place NE, Minneapolis, USA) were measured by ELISA using a commercially available kit. The detection range for IL-6 was 1.1 to 14.3 pg/mL and for TNF-α was 0.5–16 pg/mL. The intra- and inter-assay precisions of IL-6 were 4.9% and 6%, respectively. The intra- and inter-assay precisions of TNF-α were 4.3% and 7.2%, respectively.

Red blood cell (RBC) samples were washed with normal saline after removing the plasma. Then, the RBCs were diluted with 25 × sodium phosphate buffer for superoxide dismutase (SOD) and glutathione peroxidase (GPx) measurements, and with 250 × sodium phosphate buffer for catalase (CAT) measurement. The antioxidant enzymes activities (CAT, SOD, and GPx) were determined using fresh samples and the methods for measuring these activities have been described previously [15–17]. The protein content of the plasma and RBCs was determined based on the biuret reaction of the bicinchoninic acid kit (Thermo, Rockford, IL, USA). The values for the antioxidant enzymes activities were expressed as units/mg of protein. All of the analyses were performed in duplicate.

Statistical analyses

The data were analyzed using the SigmaPlot software package (version 12.0, Systat, San Jose, CA, USA). The normal distribution of variables was tested by the Kolmogorov-Smirnov test. Differences in participants' demographic data and the hematologic measurements between the placebo and LC groups were analyzed by Student's *t* test or the Mann-Whitney rank-sum test. The paired *t* test or Wilcoxon signed rank test was used to analyze the data within each group before (baseline) and after intervention (week 12). For the categorical response variables, differences between the two groups were assessed by the χ^2 test or Fisher's exact test. To examine the correlations between the levels of inflammation markers, oxidative stress, and antioxidant enzymes activities after LC supplementation, the Pearson product moment correlations were used. The results were considered statistically significant at $P < 0.05$. Values presented in the text are means ± SD.

Results

Study participant characteristics

The sampling and trial profiles are summarized in Figure 1, along with the number of participants who completed the study in each group. Table 1 presents the demographic data and the health characteristics of the participants at the baseline. There were no significant differences between the two groups with respect to age, blood pressure, anthropometric measurements, hematologic entities (serum creatinine and lipid profiles), and the frequency of smoking, drinking, or exercise at baseline.

Effects of LC supplementation on levels of inflammation markers

The levels of inflammation markers after supplementation are shown in Table 2. After 12 wk of LC supplementation, the participants in the LC group had significantly lower levels of inflammation markers than at baseline (CRP, $P < 0.01$; IL-6, $P = 0.03$, TNF-α, $P = 0.07$) and than those in the placebo group (CRP, $P < 0.05$; IL-6, $P = 0.04$, TNF-α, $P = 0.03$). The changed levels of CRP ($P = 0.04$), IL-6 ($P < 0.05$), and TNF-α ($P = 0.04$) were significantly lower in the LC group than in the placebo group.

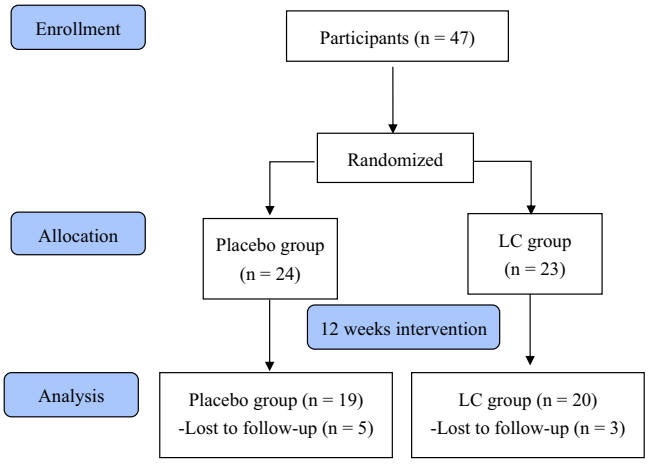

Fig. 1. Flow diagram. LC, L-carnitine.

Table 1
Participant characteristics at baseline*

	Placebo (n = 19)	LC (n = 20)	*P* values†
Sex (male)	19	20	–
Age (y)	72.7 ± 10.1 (74)	71.9 ± 10.6 (72)	0.80
Systolic blood pressure (mm Hg)	127.3 ± 6.0 (128)	128.4 ± 10.4 (130)	0.68
Diastolic blood pressure (mm Hg)	74.5 ± 4.4 (74)	72.3 ± 4.7 (71)	0.22
Waist circumference (cm)	97.7 ± 11.4 (96)	91.4 ± 8.4 (91.5)	0.08
Waist–hip ratio	0.9 ± 0.1 (0.9)	0.9 ± 0.1 (0.9)	0.09
Body mass index (kg/m^2)	26.0 ± 2.4 (25.6)	24.8 ± 2.6 (24.6)	0.16
Creatinine (μmol/L)	106.1 ± 44.2 (97.2)	114.9 ± 26.5 (106.1)	0.33
Total cholesterol (mmol/L)	5.0 ± 1.2 (4.6)	4.9 ± 0.7 (4.9)	0.76
Triacylglycerol (mmol/L)	1.7 ± 0.7 (1.6)	1.4 ± 0.7 (1.1)	0.13
Low-density lipoprotein cholesterol (mmol/L)	3.0 ± 1.3 (3)	3.0 ± 0.7 (3.1)	0.97
High-density lipoprotein cholesterol (mmol/L)	1.2 ± 0.2 (1.2)	1.4 ± 0.4 (1.3)	0.10
Current smoker‡, n (%)	3 (15.8)	4 (20)	1.00
Drink alcohol§, n (%)	3 (15.8)	3 (15)	1.00
Exercise‖, n (%)	17 (89.5)	20 (100)	0.23

LC, L-carnitine
* Mean ± SD (median).
† Values are significantly different between placebo and LC groups.
‡ Current smoker: individual currently smokes ≥1 cigarette/d.
§ Drink alcohol: individual drinks ≥1 drink/d regularly.
‖ Exercise: individual exercises at ≥3 times/wk.

Correlations between levels of inflammation markers, LC, and antioxidant status after supplementation

The correlations between the levels of inflammation markers, LC, and antioxidant status after supplementation are shown in Table 3. After 12 wk of supplementation, the level of TNF-α was significantly negatively correlated with the level of LC ($r = -0.30$; $P = 0.02$). The levels of CRP and IL-6 were significantly positively correlated with MDA and the levels of CRP, IL-6, and TNF-α negatively correlated with antioxidant enzymes activities (SOD and GPx).

Discussion

To our knowledge, this is the first clinical study to examine the antiinflammation effect of LC supplementation in patients with CAD. In this clinical trial, we demonstrated that LC at a dose of 1000 mg/d for 12 wk significantly reduced the levels of inflammation markers in patients with CAD. The levels of LC and antioxidant enzymes activities were significantly negatively correlated with inflammation markers (Table 3). Based on these results, it seems that LC has an antiinflammation effect in CAD that may be related to its antioxidant capacity.

Recent in vivo and in vitro studies have demonstrated that LC can prevent oxidative injury in cardiovascular disease models, including reducing lipid peroxidation, scavenging hydrogen peroxide and superoxide radicals, chelating transition metal ions [18–22], and up-regulating the endogenous antioxidant defense system, such as increasing CAT, SOD, and GPx activities [23–26]. A previous study [27] showed that LC might be a good antioxidant supplement for CAD. After 12 wk of LC supplementation, the level of MDA was significantly reduced (2.0 ± 0.3 to 1.8 ± 0.3 μmol/L, $P = 0.02$) and the level of LC (33.6 ± 13.6 to 40.0 ± 12.0 μmol/L, $P = 0.04$) and antioxidant enzymes activities (CAT [12.7 ± 5.5 to 13.1 ± 5.8 U/mg of protein, $P = 0.02$], SOD [14.8 ± 2.9 to 20.7 ± 5.8 U/mg of protein, $P < 0.01$], and GPx [20.3 ± 3.4 to 23.0 ± 3.1 U/mg of protein, $P = 0.01$]) were significantly increased, compared with baseline. It is already known that inflammation

Table 2
Levels of inflammation markers after supplementation*

	Placebo (n = 19)		LC (n = 20)		*P* values†
	Means ± SD (median)	Range*	Means ± SD (median)	Range	
Week 0					
CRP (mg/L)	2.2 ± 3.6 (1.10)	0.03–1.6	2.2 ± 2.9 (1.00)	0.02–1.0	0.65‡
IL-6 (pg/mL)	1.5 ± 0.6 (1.54)	1.0–3.0	1.6 ± 0.6 (1.40)	0.8–2.8	0.72‡
TNF-α (pg/mL)	1.9 ± 1.9 (1.29)	0.9–9.6	2.1 ± 1.3 (1.56)	0.8–5.4	0.34‡
Week 12					
CRP (mg/L)	3.9 ± 6.1 (2.00)	0.02–2.6	1.2 ± 1.3 (1.00)§	0.02–0.6	<0.05‡,§
IL-6 (pg/mL)	1.8 ± 1.1 (1.40)	0.8–5.1	1.3 ± 0.4 (1.15)§	0.9–2.3	0.04‡
TNF-α (pg/mL)	2.4 ± 2.1 (1.69) ‡	1.3–9.7	1.8 ± 0.8 (1.52)	1.0–4.0	0.03‡
Week 12–0					
CRP (mg/L)	2.0 ± 7.0 (0.06)	−1.5 to 2.4	−1.1 ± 2.4 (−0.10)	−0.9 to 0.2	0.04‡
IL-6 (pg/mL)	0.3 ± 0.9 (−0.01)	−0.8 to 3.2	−0.4 ± 0.6 (−0.24)	−1.6 to 0.8	<0.05‡,‖
TNF-α (pg/mL)	0.3 ± 0.3 (0.16)	−0.2 to 0.9	0.1 ± 0.2 (0.10)	−0.3 to 0.6	0.04¶

CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor
* Minimum–maximum.
† Values are significantly different between the placebo and LC groups.
‡ Data were analyzed by the Mann-Whitney rank-sum test.
§ Values were significantly different after intervention within the group: $P = 0.047$.
‖ Values were significantly different after intervention within the group: $P = 0.045$.
¶ Data were analyzed by the Student's *t* test.

Table 3
Correlations between levels of inflammation markers, L-carnitine, and antioxidant status after supplementation

	Inflammation markers (r*, P values)		
	CRP (mg/L)	IL-6 (pg/mL)	TNF-α (pg/mL)
LC (μmol/L)	−0.001 (0.99)	−0.004 (0.97)	−0.295 (0.02)
MDA (μmol/L)	0.529 (<0.01)	0.523 (<0.01)	−0.207 (0.10)
CAT (U/mg protein)	−0.078 (0.49)	−0.055 (0.63)	−0.068 (0.59)
SOD (U/mg protein)	−0.243 (0.03)	−0.183 (<0.05)	−0.197 (0.05)
GPx (U/mg protein)	−0.331 (<0.01)	−0.312 (<0.01)	−0.191 (0.06)

CAT, catalase activity; CRP, C-reactive protein; GPx, glutathione peroxidase; IL, interleukin; LC, L-carnitine; MDA, malondialdehyde; SOD, superoxide dismutase; TNF, tumor necrosis factor
* Correlation coefficients.

may be triggered by the reactive oxygen species (ROS), which up-regulates the expression of proinflammatory cytokines, and then actives the NF-κB pathway [28]. NF-κB is a ubiquitous transcription factor and pleiotropic regulator of numerous genes involved in the immune and inflammatory responses [29]. Studies have indicated that the NF-κB activating cascade can be inhibited by antioxidants, such as LC [30,31]. Therefore, LC may suppress the formation of ROS, resulting in inhibition of the NF-κB pathway [8,9,32]. One study [8] recently indicated that the antiinflammation effect of LC not only inhibited NF-κB activity but also suppressed nitric oxide and inducible nitric oxide synthase production, which have been implicated in the pathogenesis of inflammation diseases. As a result, LC could be an antiinflammation supplement in patients with chronic inflammation, such as patients with CAD.

In recent years, two clinical studies have demonstrated that LC supplementation (20 mg/kg) can reduce the level of CRP in patients on hemodialysis [10,11]. Another two clinical studies provided the hemodialysis patients with LC supplementation at dose of 1000 mg/d for 12 wk, and the level of inflammation markers, such as serum amyloid A, showed a significant decrease of 32% ($P < 0.01$) [13], CRP and IL-6 showed a significant decrease of 29% ($P < 0.05$) and 61% ($P < 0.001$), respectively [12]. However, it has been reported that LC supplementation at dose of 2000 mg/d had no significant effect on the levels of inflammation markers in healthy individuals [33]. This lack of an effect in healthy individuals may be caused by the fact that they do not have high levels of inflammation. Of the participants in the present study, 54% had a high inflammation status according to CRP levels (≥1 mg/L), 49% according to IL-6 levels (≥0.5 pg/mL), and 59% according to TNF-α levels (≥1.4 pg/mL). On average, >50% of our participants with CAD showed a high inflammation status. After 12 wk, LC supplementation at dose of 1000 mg/d significantly reduced the levels of CRP by 10%, IL-6 by 17%, and TNF-α by 6%, respectively, compared with baseline. Two clinical studies [34,35] showed some clinical benefits in a lower dose of LC supplementation (500 mg/d) in patients with migraine and those on chronic hemodialysis, but these studies did not examine the antiinflammatory effect and not used LC supplementation alone. Atherosclerosis is considered a chronic inflammatory disease; to lower the inflammation status in CAD, we suggest that LC supplementation at dose of 1000 mg/d may suppress the inflammation response in CAD, especially in those with a high inflammation and oxidative stress. However, further study is worthwhile to investigate an antiinflammation effect with a lower dose of LC supplementation combined with other antioxidant vitamins in patients with CAD.

A recent review suggested that LC supplementation (500–1000 mg/d) could be initiated in participants with a lower LC reference value (20 μmol/L) [36]. The main functions of LC are esterified and transport long-chain fatty acids through the mitochondrial membrane [6,7]. When fatty acid oxidation is impaired, acyl-coenzyme A may accumulate and deplete the coenzyme A intramitochondrial pool, causing a generalized mitochondrial dysfunction and multiorgan failure [36]. Although our patients with CAD did not have carnitine depletion at baseline (<20 μmol/L), inflammation status was significantly decreased after 12 wk of LC supplementation at dose of 1000 mg/d.

Many clinical studies have reported no major clinical toxicity after a higher LC supplementation (2000–4000 mg/d) [37–40]. A well-known study reported that a higher LC level (>45.1 μmol/L) may increase the risk for cardiovascular disease [41], although these results are controversial [42]. The administered dose of LC (1000 mg/d) in the present study was within dietary supplementation dose (the Ministry of Health and Welfare in Taiwan recommends a daily dietary intake of ≤2000 mg of LC). As the dose of LC supplementation (1000 mg/d) was not a pharmacologic dose, it can be expected that LC would not promote atherosclerosis or compromise cardiovascular health [42]. In this study, we provided patients with CAD with LC at a dose of 1000 mg/d divided into two doses (500 mg twice daily) and there were no clinically significant changes in the participants' vital signs and hematologic values were within the normal ranges (such as blood urea nitrogen, creatinine, glutamic oxaloacetic transaminase, and glutamic pyruvate transaminase) after 12 wk supplementation; this result means that LC at a dose of 1000 mg/d had no renal or liver toxicity. There were no serious adverse events, no complaints of side effects such as nausea and vomiting [43], and no withdrawals due to adverse events. Based on the results, we support that LC at dose of 1000 mg/d had a protective effect on patients with CAD.

There are two limitations of the present study that should be mentioned. First, the number of participants was small, although we did recruit more participants than expected. Second, this study was designed using daily LC supplementation for only 12 wk. Larger and longer intervention studies are required to better explore this potential CAD therapy.

In conclusion, we have demonstrated that LC supplementation at a dose of 1000 mg/d significantly reduced inflammation status in patients with CAD. LC has an antiinflammatory effect in CAD that could be attributed to its role as an antioxidant.

Acknowledgments

The authors acknowledge the patients for their participation and Dr. Hsia, who kindly provided the supplements for this trial. They acknowledge the nurses at Taichung Veterans General Hospital for providing expert assistance in blood sample collection and data analysis.

References

[1] Tracy RP. Inflammation in cardiovascular disease: cart, horse or both-revisited. Arterioscler Thromb Vasc Biol 2002;22:1514–5.
[2] Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340:115–26.
[3] Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk future myocardial infarction among apparently healthy men. Circulation 2000;101:1767–72.
[4] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
[5] Gurrola-Díaz CM, Sánchez-Enriquez S, Oregon-Romero E, García-López PM, Garzón de la Mora P, Bastidas-Ramírez BE, et al. Establishment of a cut-

point value of serum TNF-alpha levels in the metabolic syndrome. J Clin Lab Anal 2009;23:51–6.
[6] Kendler BS. Carnitine: an overview of its role in preventive medicine. Prev Med 1986;15:373–90.
[7] Flanagan JL, Simmons PA, Vehige J, Willcox MD, Garrett Q. Role of carnitine in disease. Nutr Metab 2010;7:30.
[8] Koc A, Ozkan T, Karabay AZ, Sunguroglu A, Aktan F. Effect of L-carnitine on the synthesis of nitric oxide in RAW 264 A7 murine macrophage cell line. Cell Biochem Funct 2011;29:679–85.
[9] Moeinian M, Ghasemi-Niri SF, Mozaffari S, Abdollahi M. Synergistic effect of probiotics, butyrate and L-Carnitine in treatment of IBD. JMHI 2013;7:50–3.
[10] Savica V, Santoro D, Mazzaglia G, Ciolino F, Monardo P, Calvani M, et al. L-carnitine infusions may suppress serum C-reactive protein and improve nutritional status in maintenance hemodialysis patients. J Ren Nutr 2005;15:225–30.
[11] Duranay M, Akay H, Yilmaz FM, Senes M, Tekeli N, Yücel D. Effects of L-carnitine infusions on inflammatory and nutritional markers in haemodialysis patients. Nephrol Dial Transplant 2006;21:3211–4.
[12] Shakeri A, Tabibi H, Hedayati M. Effects of L-carnitine supplement on serum inflammatory cytokines, C-reactive protein, lipoprotein (a), and oxidative stress in hemodialysis patients with Lp (a) hyperlipoproteinemia. Hemodial Int 2010;14:498–504.
[13] Tabibi H, Hakeshzadeh F, Hedayati M, Malakoutian T. Effects of L-carnitine supplement on serum amyloid A and vascular inflammation markers in hemodialysis patients: a randomized controlled trial. J Ren Nutr 2011;21:485–91.
[14] Botsoglou NA. Rapid, sensitive, and specific thiobarbituric acid method for measuring lipid peroxidation in animal tissue, food and feedstuff samples. J Agric Food Chem 1994;42:1931–7.
[15] Paglia D, Valentine W. Studies on the qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin Med 1967;70:159–69.
[16] Marklund S, Marklund G. Involvement of superoxide anion radical in autoxidation of pyrogallol and a convenient assay for superoxide dismutase. Eur J Biochem 1974;47:469–74.
[17] Aebi H. Catalase in vitro. Methods Enzymol 1984;105:121–6.
[18] Lysiak W, Lilly K, DiLisa F, Toth PP, Bieber LL. Quantitation of the effect of L-carnitine on the levels of acid-soluble short-chain acyl-CoA and CoASH in rat heart and liver mitochondria. J Biol Chem 1988;263:1151–6.
[19] Broderick TL, Quinney HA, Lopaschuk GD. Carnitine stimulation of glucose oxidation in the fatty acid perfused isolated working rat heart. J Biol Chem 1992;267:3758–63.
[20] Gülçin I. Antioxidant and antiradical activities of L-carnitine. Life Sci 2006;78:803–11.
[21] Kolodziejczyk J, Saluk-Juszczak J, Wachowicz B. L-Carnitine protects plasma components against oxidative alterations. Nutrition 2011;27:693–9.
[22] Mingorance C, Rodríguez-Rodríguez R, Justo ML, Alvarez de Sotomayor M, Herrera MD. Critical update for the clinical use of L-carnitine analogs in cardiometabolic disorders. Vasc Health Risk Manag 2011;7:169–76.
[23] Binienda ZK, Ali SF. Neuroprotective role of L-carnitine in the 3-nitropropionic acid induced neurotoxicity. Toxicol Lett 2001;125:67–73.
[24] Augustyniak A, Skrzydlewska E. The influence of L-carnitine supplementation on the antioxidative abilities of serum and the central nervous system of ethanol-induced rats. Metab Brain Dis 2010;25:381–9.
[25] Miguel-Carrasco JL, Monserrat MT, Mate A, Vázquez CM. Comparative effects of captopril and l-carnitine on blood pressure and antioxidant enzyme gene expression in the heart of spontaneously hypertensive rats. Eur J Pharmacol 2010;632:65–72.
[26] Li JL, Wang QY, Luan HY, Kang ZC, Wang CB. Effects of L-carnitine against oxidative stress in human hepatocytes: involvement of peroxisome proliferator-activated receptor alpha. J Biomed Sci 2012;19:32.
[27] Lee BJ, Lin JS, Lin YC, Lin PT. Effects of L-carnitine supplementation on oxidative stress and antioxidant enzymes activities in patients with coronary artery disease: a randomized, placebo-controlled trial. Nutr J 2014;13:79.
[28] Setia S, Sanyal SN. Nuclear factor kappa B: a pro-inflammatory, transcription factor-mediated signaling pathway in lung carcinogenesis and its inhibition by nonsteroidal antiinflammatory drugs. J Environ Pathol Toxicol Oncol 2012;31:27–37.
[29] Siomek A. NF-κB signaling pathway and free radical impact. Acta Biochim Pol 2012;59:323–31.
[30] Conner EM, Grisham MB. Inflammation, free radicals, and antioxidants. Nutrition 1996;12:274–7.
[31] Kurutas EB, Cetinkaya A, Bulbuloglu E, Kantarceken B. Effects of antioxidant therapy on leukocyte myeloperoxidase and Cu/Zn-superoxide dismutase and plasma malondialdehyde levels in experimental colitis. Mediators Inflamm 2005;2005:390–4.
[32] Cetinkaya A, Bulbuloglu E, Kantarceken B, Ciralik H, Kurutas EB, Buyukbese MA, et al. Effects of L-carnitine on oxidant/antioxidant status in acetic acid-induced colitis. Dig Dis Sci 2006;51:488–94.
[33] Volek JS, Judelson DA, Silvestre R, Yamamoto LM, Spiering BA, Hatfield DL, et al. Effects of carnitine supplementation on flow-mediated dilation and vascular inflammatory responses to a high-fat meal in healthy young adults. Am J Cardiol 2008;102:1413–7.
[34] Tarighat Esfanjani A, Mahdavi R, Ebrahimi Mameghani M, Talebi M, Nikniaz Z, Safaiyan A. The effects of magnesium, L-carnitine, and concurrent magnesium-L-carnitine supplementation in migraine prophylaxis. Biol Trace Elem Res 2012;150:42–8.
[35] Tayebi Khosroshahi H, Habibi Asl B, Habibzadeh A, Chaichi P, Ghanbarpour A, Hossein Badie A. Comparison of vitamin e and L-carnitine, separately or in combination in patients with intradialytic complications. Nephrourol Mon 2013;5:862–5.
[36] Bonafé L, Berger MM, Que YA, Mechanick JI. Carnitine deficiency in chronic critical illness. Curr Opin Clin Nutr Metab Care 2014;17:200–9.
[37] Rubin MR, Volek JS, Gomez AL, Ratamess NA, French DN, Sharman MJ, et al. Safety measures of L-carnitine L-tartrate supplementation in healthy men. J Strength Cond Res 2001;15:486–90.
[38] Cruciani RA, Dvorkin E, Homel P, Malamud S, Culliney B, Lapin J, et al. Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: a phase I/II study. J Pain Symptom Manage 2006;32:551–9.
[39] Puskarich MA, Kline JA, Krabill V, Claremont H, Jones AE. Preliminary Safety and Efficacy of L-carnitine Infusion for the Treatment of Vasopressor-Dependent Septic Shock: a randomized control trial. J Parenter Enteral Nutr 2013;20:1–8.
[40] Zhang W, Li P, Cai ZK, Zheng JH, Dai JC, Wang YX, et al. Safety and efficacy of L-carnitine and tadalafil for late-onset hypogonadism with ED: a randomized controlled multicenter clinical trial. Zhonghua Nan Ke Xue 2014;20:133–7.
[41] Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013;19:576–85.
[42] McCarty MF. L-carnitine consumption, its metabolism by intestinal microbiota, and cardiovascular health. Mayo Clin Proc 2013;88:786–9.
[43] Singh RB, Aslam M. L-carnitine administration in coronary artery disease and cardiomyopathy. J Assoc Physicians India 1998;46:801–5.