L-Carnitine Increases High Density Lipoprotein-Cholesterol in Healthy Individuals: a Randomized Trial

ABSTRACT

Background/Objective: the popular use of L-carnitine (LC) as a food supplement for patients with diverse disorders is based on the antioxidant, anti-inflammatory and hypolipidemic properties of the amino acid. Since no clinical studies have focused on the effects of LC supplementation in healthy subjects, our objective was to determine whether daily administration of LC to adults presenting no morbidities would induce changes in their glycemic, lipid or inflammatory status. **Methods**: thirty healthy volunteers aged between 19 and 52 years were divided randomly into two equal groups, one of which received 1000 mg of LC per day over a 12-week period while the other received a corresponding dose of identical matching placebo. Serum levels of glucose, total cholesterol, high- and low-density lipoprotein cholesterol (HDL-C and LDL-C, respectively), triglycerides, apolipoprotein A1 (ApoA1) and C-reactive protein were assessed before and after intervention. **Results:** total cholesterol and HDL-C increased significantly ($p < 0.05$) after supplementation with LC but not with placebo. A strong, statistically significant inverse correlation between triglycerides and HDL-C was detected after supplementation with LC but not with placebo. Strong and significant direct correlations between HDL-C and ApoA1 were observed in both groups before and after intervention. No significant correlations between LDL-C and HDL-C or triglycerides and glucose were observed in either group. **Conclusions:** the significant increase in HDL-C observed in healthy adults after LC supplementation indicates that the nutraceutical could be useful in impeding the development of heart diseases in subjects with low HDL-C.

Keywords: Cardiovascular risk, L-Carnitine supplementation, Lipid profile, High-density lipoprotein cholesterol, Apolipoprotein A1

1. INTRODUCTION

L-carnitine (LC), the biologically active isomer of carnitine, is a derivative of the amino acid L-lysine that is biosynthesized naturally by the human body and may also be absorbed from dietary intake. Although healthy individuals generally synthesize sufficient LC for their daily needs, patients with carnitine deficiency caused by, for example, diabetes, cardiomyopathy, malnutrition, cirrhosis, and renal, endocrine or neural disorders, may require LC in the form of a nutritional supplement [1]. LC is also employed as an adjuvant in the treatment of obesity and dyslipidemias because of its role as a transporter of long-chain fatty acids across the inner mitochondrial membrane and their subsequent β-oxidation.

Alongside the importance of LC in lipid metabolism and energy production, there is evidence that the amino acid reduces metabolic stress induced by reactive oxygen species and is, therefore, potentially useful in the control of inflammatory processes [2, 3]. Furthermore, in view of the association between oxidative stress, inflammation, hyperlipidemia and coronary artery disease (CAD), it has been suggested that the exogenous administration of LC may be beneficial to individuals presenting CAD or risk factors for this condition [4-6].

In consideration of the above, it is understandable that most research on LC supplementation has targeted individuals with cardiometabolic diseases, while little attention has been given to the potential of LC as a non-pharmacological nutritional supplement for healthy individuals that could help prevent or control the development of dyslipidemia and its severe consequences. In this context, we postulate that supplementation of LC to healthy subjects would lead to changes in their glycemic, lipid and inflammatory status. The objectives of this study were, therefore, to determine the levels of serum biomarkers of hyperglycemia, lipid metabolism and inflammation before and after the administration of LC or identical matching placebos to adults presenting no morbidities, and to investigate possible correlations between paired biomarkers in LC and placebo groups.

2. Materials And Methods

The randomized, double-blind, placebo-controlled, parallel-group trial involved 30 healthy volunteers recruited at the Outpatients Department of the Cardiology Clinic of Hospital São José do Avaí, Itaperuna, Rio de Janeiro, Brazil, between May and July 2018. The sample size was calculated: groups with 13 participants were found to be more statistically powerful (90%) than those with 11 (85%) and 10 (80%), all of them were statistically significant ($p < 0,05$). Inclusion criteria were clinically healthy adults aged between 18 and 60 years, who did not use any medication or food supplements that could interfere with lipid metabolism.

All participants volunteered to participate in the trial and signed the appropriate Informed Consent Form containing specific information about the study.

Volunteers were distributed randomly into two groups (each comprising 15 individuals), one of which received LC supplement and the other identical matching placebo. Randomization of subjects into LC and placebo groups was performed by a statistician, in which all participants were placed in alphabetical order and numbered from 1 to 30. The LC group comprised subjects with odd numbers, while the remaining subjects were placed in the placebo group.

A pharmacist with no knowledge of the subjects or groups prepared sets of identical flasks containing either two 500 mg capsules of LC or two 500 mg capsules containing only excipient, and each set of flasks was ascribed to and labeled with the name of the subject in accord with a randomized scheme known only to the statistician. Sets of flasks containing daily doses of 1000 mg (two capsules) of LC/placebo were delivered to individuals at the Cardiology Clinic by a third person who had no knowledge about the content of the flasks, the identities of the subjects or their groups. The trial lasted for a total of 12 weeks, during which period individuals were expected to return to the Cardiology Clinic every four weeks to receive a further supply of capsules and to confirm adherence to the regime.

2.1 Biochemical analysis

The participants were asked to fast for 12 h, not perform vigorous physical activity for 24 h and not drink alcohol 72 h before collection of blood. Peripheral blood was collected by venipuncture from each participant immediately prior to supplementation with LC or placebo and 12 weeks after the start of the trial. Blood samples were allowed to clot and serum was separated by centrifugation at 2500 rpm for 10 min. Fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides were determined enzymatically using commercial assay kits (Kovalent, São Gonçalo, RJ, Brazil) and an Architect c8000 automatic analyzer (Abbott, Chicago, IL, USA). Low-density lipoprotein cholesterol (LDL-C) was calculated from total cholesterol, HDL-C and triglycerides levels using Friedewald's formula. Levels of apolipoprotein A1 (ApoA1) and C-reactive protein (CRP) were estimated

by immunoturbidimetry. All analyses were carried out in the Laboratory of Clinical Analysis at Universidade Iguaçu, Itaperuna, RJ, Brazil.

2.2 STATISTICAL ANALYSIS

Data were evaluated according to descriptive statistics, namely minimum, maximum, median, mean ± standard deviation (SD) and percentage. The Kolmogorov-Smirnov test for normality was applied to establish whether variables were normally distributed, and the Student's t and Mann Whitney tests were used to compare values obtained before and after administration of supplements. In all analyses, the statistical significance was set at $p< 0.05$. Correlations between glycemic and/or lipid biomarkers in the LC and placebo groups were investigated using Person's correlation coefficient (r) with the strength of relationships defined according to the value of r as follows: 0.00 to 0.30 (negligible), 0.30 to 0.50 (weak), 0.50 to 0.70 (moderate), 0.70 to 0.90 (strong) and 0.90 to 1.00 (very strong) [8].

3. RESULTS AND DISCUSSION

The LC and placebo groups were comparable in terms of age (range 19 to 52 years), gender, body mass index, smoking habits and lifestyle (Table 1). All participants adhered fully to the prescribed treatment and were analyzed for the primary outcome without losses.

Table 1 - Characteristics of the study population of healthy individuals

Parameter	L-Carnitine group (n = 15)	Placebo group (n = 15)
Age (years; mean ± standard deviation)	34.3 ± 5.7	33.3 ± 9.5
Body mass index (kg/m2)	24.6 ± 3.8	25.0 ± 4.2
Gender ratio (male/female)	4/11	5/10
Smoking habit (%)	0	13.3
Sedentary lifestyle (%)	20	13.3

There were no significant differences ($p> 0.05$) between the two groups.

In the LC group, levels of total cholesterol and HDL-C increased significantly after supplementation (13 and 25%, respectively; $p< 0.05$) in comparison with values obtained before treatment, while glucose levels showed a slight, but significant, reduction (9%; $p < 0.05$) after treatment (Table 2). The levels of LDL-C, ApoA1, triglycerides and CRP assessed before and after LC supplementation showed no significant variations ($p > 0.05$). In the placebo group, glucose levels showed a modest, but significant, reduction (10%; $p< 0.05$; Table 2) following supplementation but values of the lipid parameters and CRP showed no significant variation after treatment.

Table 2 - Effects of L-carnitine supplementation over a 12-week period on the glycemic, lipid and inflammatory status of healthy individuals

Parameter	L-Carnitine group (n = 15)			Placebo group (n = 15)		
	Before supplementation	After supplementation	p	Before supplementation	After supplementation	p
Glucose (mg/dL)	86.1 ± 10.3	78.1 ± 8	<0.05	89.2 ± 10.7	79.8 ± 6	<0.05
Total cholesterol (mg/dL)	152 ± 21.3	172.3 ± 31	<0.05	167.9 ± 41.1	177.8 ± 51.8	>0.05
HDL-C (mg/dL)	54.3 ± 13.1	68.2 ± 17.5	<0.05	60.5 ± 13.4	60.6 ± 18.8	>0.05
LDL-C (mg/dL)	81.3 ± 17.3	86.7 ± 32.3	>0.05	92.8 ± 32.4	102 ± 46.1	>0.05
Triglycerides(mg/dL)	82.5 ± 45.6	86.9 ± 40.1	>0.05	72.3 ± 31.9	78.3 ± 41.5	>0.05
ApoA1 (mg/dL)	143.7 ± 27.1	159.1 ± 22.8	>0.05	149.5 ± 34.4	146.4 ± 43	>0.05
CRP (mg/L)	0.13 (0.03–1.6)	0.18 (0.01–1.5)	>0.05	0.29 (0.02-2.1)	0.22 (0.03-2.9)	>0.05

Data are expressed as mean values ± standard deviation and compared using Student's t test, except for CRP data that are expressed as median values (minimum-maximum) and compared using Mann-Whitney test. Differences were considered significant for p < 0.05.

Correlation analysis revealed that there were significant ($p < 0.05$) inverse linear associations in the LC group between levels of triglycerides and HDL-C that varied from moderate before ($r = -0.60$; Fig. 1a) to strong after ($r = -0.82$; Figs.1c) supplementation. In contrast, significant ($p < 0.05$) direct linear associations were detected between HDL-C and ApoA1 that varied from strong before ($r = 0.89$; Fig. 2a) to be very strong after ($r = 0.91$; Fig.2c) supplementation. On the other hand, correlations between LDL-C and HDL-C (Figs. 2a and 2c) and between triglycerides and glucose (Figs. 3a and 3c) in the LC group both before and after supplementation were not significant ($p > 0.05$) and varied from negligible to weak. In the placebo group, correlations between triglycerides and HDL-C (Figs. 1b and 1d), between LDL-C and HDL-C (Figs. 2b and 2d) and between triglycerides and glucose (Figs. 3b and 3d) were not statistically significant and varied from negligible to weak both before and after supplementation. However, significant ($p < 0.05$) direct linear associations were detected between levels of HDL-C and ApoA1 in the placebo group and these varied from moderate before ($r = 0.56$; Fig. 4b) to very strong after ($r = 0.97$; Fig. 4d) supplementation.

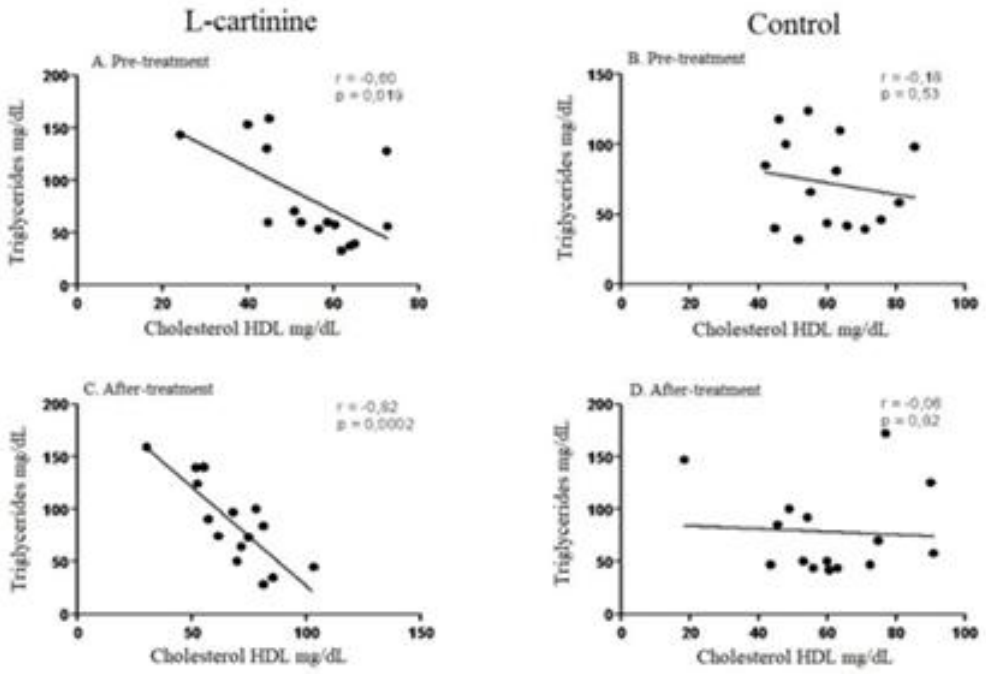

Figure 1 - Scatter plots showing associations between triglycerides and high-density lipoprotein cholesterol (HDL-C) before (a and b) and after (c and d) supplementation with L-carnitine or placebo.

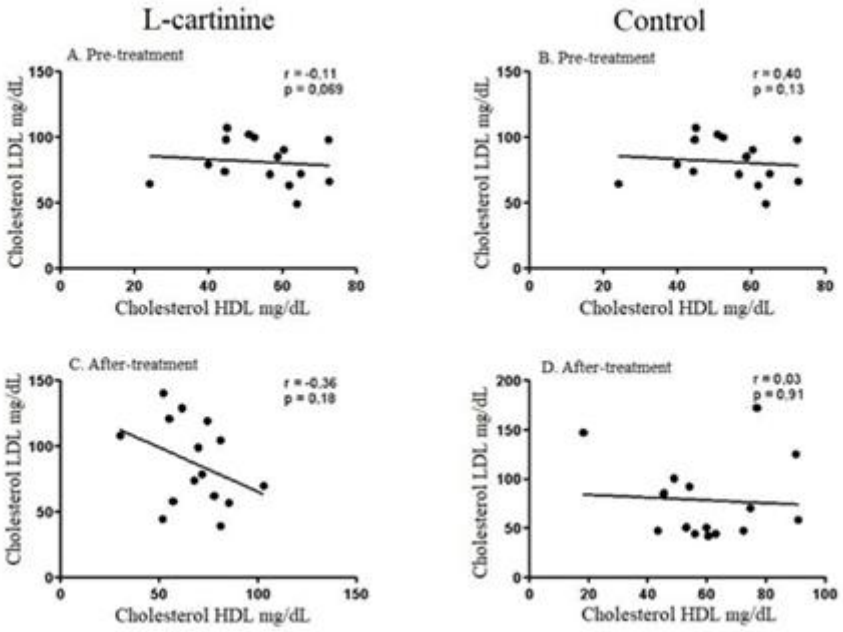

Figure 2 - Scatter plots showing associations between low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) before (a and b) and after (c and d) supplementation either with L-carnitine or placebo.

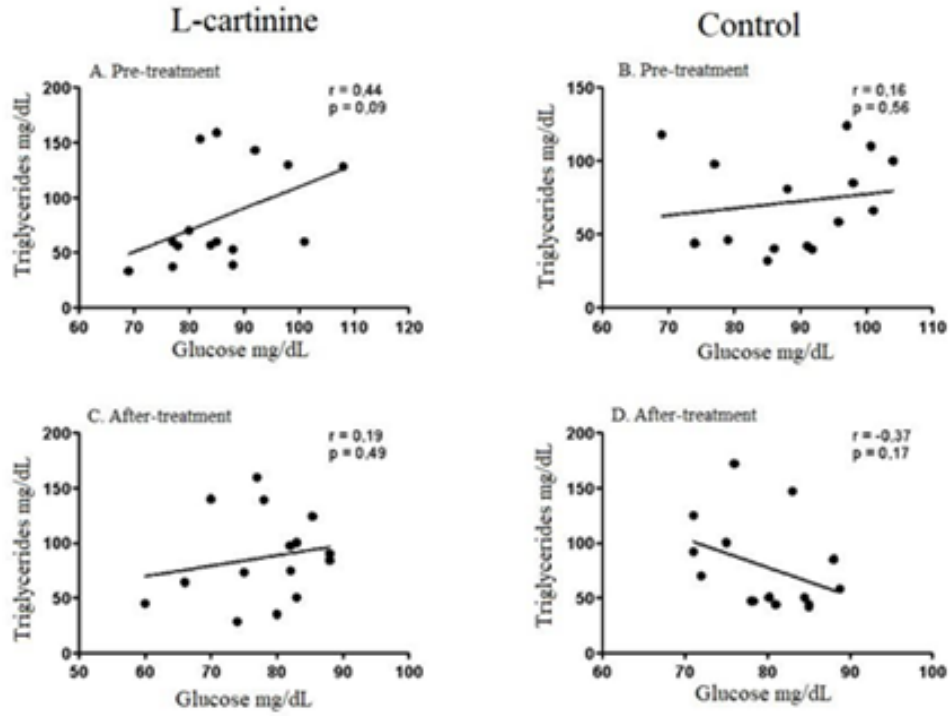

Figure 3 - Scatter plots showing associations between triglycerides and glucose before (a and b) and after (c and d) supplementation with L-carnitine or placebo.

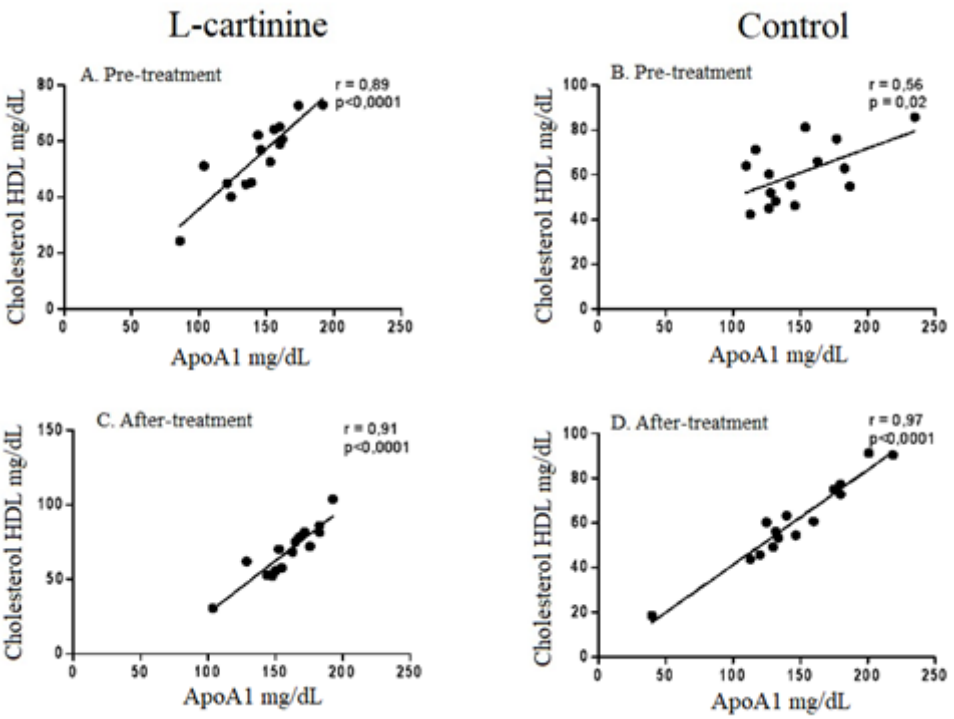

Figure 4 - Scatter plots showing associations between ApoA1 and high-density lipoprotein cholesterol (HDL-C) before (a and b) and after (c and d) supplementation with L-carnitine or placebo.

4. DISCUSSION

After 12 weeks of daily supplementation with 1000 mg of LC, the levels of total cholesterol and HDL-C in healthy subjects increased by 13 and 25%, respectively, although no alterations were observed in the levels of LDL-C, triglycerides, ApoA1 or the inflammatory marker CRP. Correlation analysis revealed that there was a strong inverse linear relationship between triglycerides and HDL-C levels in the LC group after treatment and such association was statistically significant. On this basis, it would be anticipated that the increased levels of HDL-C observed after supplementation with LC should be accompanied by a decrease in triglycerides, but this was not observed at the dosage of LC and duration of administration employed in the experiment. Furthermore, there was a very strong, direct and statistically significant relationship between HDL-C and ApoA1 levels in the LC group after treatment implying that both biomarkers should increase concomitantly, but this was not observed in the present study.

Discrete reductions in glycemia were observed in both LC and placebo groups, suggesting that such alterations were not associated with LC supplementation but with other non-identifiable factors, like Hawthorne effect. However, Ringseis et al [9] reported that LC improved glucose tolerance, especially in insulin-resistant states, such that extra supplementation might be effective for improving glucose utilization in obese type 2 diabetic patients. Moreover, the results of the meta-analysis carried out by Vidal-Casariego et al. [10]

indicated that administration of LC gives rise to significant reductions in glucose, total cholesterol, LDL-C, and ApoA1 levels. Hence, it is possible that LC along with other factors influenced the reduction of glycemia in our study population.

The significant increases observed in total cholesterol and HDL-C levels following daily administration of LC to our population of healthy individuals are of particular interest. The anti-atherosclerotic and anti-inflammatory properties of HDL are well known and such beneficial effects have been attributed to the facilitation of reverse cholesterol transport, inhibition of lipid oxidation, reduction in the recruitment of monocytes into the artery wall, stimulation of endothelial differentiation, cell migration and reendothelialization, augmentation of angiogenesis and suppression of hematopoietic stem cell proliferation [11-16]. In addition, there is evidence that HDL modulates glucose metabolism by raising plasma insulin and activating key metabolic regulatory enzymes [17, 18]. In consideration of these cardioprotective and anti-hyperglycemic functions, a number of HDL-based therapies have been proposed for the management of CAD and type 2 diabetes mellitus.

Nevertheless, therapies that increase the concentration of HDL-C must be interpreted and applied with caution, primarily because the human HDL fraction comprises several subpopulations of particles with dissimilar sizes, densities and compositions, and with functions that are not fully understood. Since it is likely that HDL therapies exert diverse effects on the levels of the various subpopulations, it is clearly important to expand our knowledge of HDL biology and the manner in which HDL subpopulations are associated with cardioprotective properties [19, 20]. Moreover, several factors can impair the capacity of HDL to inhibit atherosclerosis and render HDL and ApoA1 dysfunctional, and these include systemic and vascular inflammation, loss of anti-inflammatory and antioxidant proteins and/or gain of pro-inflammatory proteins such as myeloperoxidase. Hence, a clearer understanding of dysfunctional HDL or ApoA1 in clinical practice would facilitate the advancement of therapies against atherosclerosis [21].

It presently remains uncertain whether therapies targeting an increase in HDL-C actually protect against atherosclerosis and reduce the risk of CAD, particularly since recent evidence suggests that the relationship between HDL-C and cardiovascular status may be more complex than previously thought. In this context, clinical trials have shown that some drugs, such as niacin and inhibitors of cholesteryl ester transfer protein, that increase HDL-C fail to reduce cardiovascular events in statin-treated subjects with confirmed CAD [22]. Moreover, the use of such agents induces other non-lipid changes that render it difficult to assess the effects of increased HDL on clinical outcomes.

Despite the rationale above, the beneficial effects of elevated levels of HDL-C cannot be disregarded considering that a large number of clinical studies have verified the inverse relationship between HDL-C and the incidence of CAD, along with the importance of HDL-C as a predictive biomarker of cardiovascular disease and mortality. Moreover, ApoA1, the structural and functional protein of HDL, has also been associated with anti-inflammatory effects and protection from atherosclerosis progression [23-28].

According to a meta-analysis performed by Asadi et al. [29], supplementation with LC, particularly in doses > 1500 mg/day, represents an alternative approach for controlling the lipid profile and glycemic status in adults presenting CAD risk factors. This analysis showed that LC supplementation caused significant changes in the levels of total cholesterol, LDL-C, HDL-C, glycemia and hemoglobin A1c, and in the homeostatic model assessment of insulin resistance (HOMA-IR). However, no significant effects of LC supplementation were observed with respect to the levels of triglycerides and ApoA1, and such findings were similar to those described in the present study.

Most previous studies involving LC supplementation have focused on the antioxidant, anti-inflammatory and hypolipidemic effects on patients with CAD [4,5] or on the capacity of the amino acid to increase exercise performance in athletes [30]. Our research is innovative for the reason that the target population consisted of healthy subjects with no cardiovascular, hepatic or renal dysfunctions. Oxidative stress is an early event in the evolution of hyperlipidemia [31], a condition that accelerates the atherosclerotic process and its morbid outcomes, and enhancement of the antioxidant capacity of healthy subjects who have an altered lipid profile (i.e. low HDL-C) may help to avert the course of the disease. On this basis, supplementation with low levels of LC may improve vascular health and reduce the dyslipidemia-induced cardiovascular risk, and could be employed as an alternative to pharmaceutical agents such as statins, as has been suggested by Scicchitano et al. [32] in regard to other nutraceuticals.

The limitations of our study are the small sample size (n = 15) employed and the impossibility of direct extrapolation of the results to cases of clinical dyslipidemia.The strengths of our work are the use of identical matching placebo controls and the duration of intervention (12 weeks), which was long enough to detect changes in the important serum markers such as HDL-C.

4. CONCLUSION

It is possible to state that dietary supplementation with 1000 mg of LC per day to healthy individuals improves levels of HDL significantly but not those of ApoA1. The significant increase in total cholesterol observed in the LC group after supplementation could be related to an enlarged HDL-C fraction, whereas the significant reduction in glycemia cannot be associated with LC supplementation alone. Triglycerides and ApoA1 were significantly and strongly correlated with HDL-C in the LC-treated group. Our study represents an original study of the effects of LC supplementation on the glycemic and lipid profiles of a healthy population, the results of which demonstrate that an inexpensive and plentiful nutraceutical could be useful in impeding the development of heart diseases in subjects with low HDL-C. It is likely that supplementation with LC would also improve glucose homeostasis in individuals diagnosed as prediabetic, although this postulation could not be fully demonstrated in the present study and requires verification.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Hospital Santa Casa de Belo Horizonte (protocol no. CAAE 90135018.7.0000.51380).

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