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ORIGINAL ARTICLE

L-Carnitine/Simvastatin Reduces Lipoprotein (a) Levels Compared with Simvastatin Monotherapy: A Randomized Double-Blind Placebo-Controlled Study

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Abstract Lipoprotein (a) [Lp(a)] is an independent risk factor for cardiovascular disease. There are currently limited therapeutic options to lower Lp(a) levels. L-Carnitine has been reported to reduce Lp(a) levels. The aim of this study was to compare the effect of L-carnitine/simvastatin co-administration with that of simvastatin monotherapy on Lp(a) levels in subjects with mixed hyperlipidemia and elevated Lp(a) concentration. Subjects with levels of low-density lipoprotein cholesterol (LDL-C) >160 mg/dL, triacylglycerol (TAG) >150 mg/dL and Lp(a) >20 mg/dL were included in this study. Subjects were randomly allocated to receive L-carnitine 2 g/day plus simvastatin 20 mg/day ($N = 29$) or placebo plus simvastatin 20 mg/day ($N = 29$) for a total of 12 weeks. Lp(a) was significantly reduced in the L-carnitine/simvastatin group [−19.4%, from 52 (20–171) to 42 (15–102) mg/dL; $p = 0.01$], but not in the placebo/simvastatin group [−6.7%, from 56 (26–108) to 52 (27–93) mg/dL, $p =$ NS *versus* baseline and $p = 0.016$ for the comparison between groups]. Similar significant reductions in total cholesterol, LDL-C, apolipoprotein (apo) B and TAG were observed in both groups. Co-administration of L-carnitine with simvastatin was associated with a significant, albeit modest, reduction in Lp(a) compared with simvastatin monotherapy in subjects with mixed hyperlipidemia and elevated baseline Lp(a) levels.

Keywords L-Carnitine · Lipoprotein (a) · Simvastatin · Triglycerides

Abbreviations

ALT	Alanine aspartate aminotransferase
ANCOVA	Analysis of covariance
apo	Apolipoprotein
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
CETP	Cholesteryl ester transfer protein
CK	Creatine phosphokinase
eGFR	Estimated glomerular filtration rate
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostasis model assessment
LDL-C	Low-density lipoprotein cholesterol
LDL-Ccor	LDL-C levels corrected for Lp(a) concentration
Lp(a)	Lipoprotein (a)
MDRD	Modification of diet in renal disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
SD	Standard deviation
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TAG	Triacylglycerol
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

Introduction

Low-density lipoprotein cholesterol (LDL-C) is the major lipoprotein promoting the development of CVD [1].

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Another highly atherogenic lipoprotein is lipoprotein (a) [Lp(a)]. Lp(a) is synthesized by the liver and contains a cholesterol rich LDL particle and apolipoprotein (apo) (a); the latter is attached to apoB-100 via a disulfide bond [2]. The levels of Lp(a) are primarily determined genetically, while dietary and environmental effects play a minor role [3–5]. Indeed, the polymorphisms of the LPA gene explain 70–90% of the variability of Lp(a) concentration [3, 6].

Current literature supports the predictive value of Lp(a) on cardiovascular [7, 8] as well as cerebrovascular outcomes, although the latter effect appears to be smaller than the former [9]. Several studies have identified increased Lp(a) levels as an independent cardiovascular, cerebrovascular and peripheral vascular disease risk factor [10–13]. Elevated Lp(a) levels have also been associated with increased risk of aortic valve stenosis in the general population, with levels >90 mg/dL predicting a threefold increased risk [14], as well as with retinopathy in diabetic patients [15]. Furthermore, Lp(a) levels seem to be a marker of restenosis after percutaneous transluminal coronary angioplasty, saphenous vein bypass graft atherosclerosis and accelerated coronary atherosclerosis of cardiac transplantation [13]. In addition, large genetic studies using the Mendelian randomization approach demonstrated that Lp(a) levels are continuously and linearly related to the risk of developing CVD [16, 17]. Of note, as much as one-fifth of the population has very elevated Lp(a) levels (>50 mg/dL) [11].

In the context of the atherogenic potential of Lp(a), the European Atherosclerosis Society recommends screening for Lp(a) in patients with moderate or high cardiovascular risk [10, 18], whereas lowering Lp(a) to a level below 50 mg/dL should be a treatment priority after the attainment of LDL-C goals [10, 18].

The effects of statins on Lp(a) levels are limited and variable [19]. Among other drugs, niacin and estrogens have been shown to decrease Lp(a), but their associated adverse effects constrain their use [10]. Novel drugs, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, cholesteryl ester transfer protein (CETP) inhibitors and antisense oligonucleotides which target apo (a) appear promising in terms of reducing Lp(a) levels and are under investigation [20–22]. Interestingly, a small number of studies have identified L-carnitine as a safe and effective way of decreasing Lp(a) as well as triacylglycerol (TAG) levels [23].

The present study was aimed to examine the safety and efficacy of L-carnitine/simvastatin combination *versus* simvastatin monotherapy on the levels of Lp(a) and other lipid and metabolic parameters in patients with mixed hyperlipidemia and elevated Lp(a) concentration at baseline.

Materials and Methods

Study Population

Fifty-eight ($N = 58$) patients 18–65 years old attending the Outpatient Lipid Clinics in four General and University Hospitals in Greece were recruited. Eligible patients had to have LDL-C >160 mg/dL, TAG >150 mg/dL and Lp(a) >20 mg/dL.

Exclusion criteria were established CVD, renal (serum creatinine levels >1.6 mg/dL), liver [alanine and/or aspartate aminotransferase levels (ALT/AST) > 3-fold upper limit of normal (ULN) in more than 2 consecutive measurements] or neoplastic disease, hypothyroidism [thyroid stimulating hormone (TSH) >5 IU/mL], history or current treatment for epileptic seizures and known hypersensitivity to simvastatin or L-carnitine. Pregnant and breastfeeding women and women of reproductive age not taking sufficient contraceptive measures, as well as patients treated with lipid-lowering drugs, diuretics, b-blockers, thyroxin, vitamin K antagonists or any drug affecting mitochondrial metabolism (e.g. benzodiazepines, glibenclamide, zidovudine) were also excluded from the study.

Study Design

This was a prospective, randomized, double-blind, placebo-controlled, parallel group, 12-week, phase IIIb clinical trial. An initial 2-week period of dietary intervention alone was mandatory for all patients and was expected to be continued throughout the entire study. The prespecified diet provided 1400–1600 kcal, 55% of which came from carbohydrates, 20–25% from proteins and 20–35% from fat (less than 7% of which was saturated). Furthermore, the diet contained less than 200 mg dietary cholesterol and up to 36 g fiber daily. After this initial period, eligible patients were randomly allocated on a 1:1 basis to treatment with simvastatin (20 mg daily) plus L-carnitine (2 g daily) or simvastatin (20 mg daily) plus placebo. Patients were instructed to take simvastatin (one sponsor provided tablet) before sleep and L-carnitine or placebo (divided into two sponsor provided bottles of 1 g soluble L-carnitine or placebo) twice daily, i.e. in the morning and before sleep.

Overall, the patients attended the Outpatient Clinic 4 times: initiation visit (2 weeks before randomization), randomization visit (week 0), a follow-up visit (week 4) and final visit (12 weeks). The study medication blisters and bottles were collected at all visits and adherence with medication was estimated by the number of used tablets and bottles. Patients were considered adherent if they took 80–100% of the prescribed number of tablets and bottles.

Table 1 Baseline characteristics of study participants

Characteristic	Simvastatin + L-carnitine ($n = 29$)	Simvastatin + placebo ($n = 29$)	p
Age (years)	53 ± 13	58 ± 5	NS
Sex (male/female)	12/17	10/19	NS
Weight (kg)	78 ± 11	75 ± 9	NS
Body mass index (kg/m^2)	29 ± 4	29 ± 4	NS
Smoking (yes/no)	13/16	11/18	NS
Systolic blood pressure (mmHg)	126 ± 10	130 ± 16	NS
Diastolic blood pressure (mmHg)	78 ± 9	81 ± 11	NS

Values are expressed as means ± SD

The primary efficacy endpoint was the difference in the change of Lp(a) levels between the two groups 12 weeks after treatment initiation. Secondary endpoints included changes from baseline in total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), TAG, apo A-I and apoB levels in the two treatment groups, as well as safety and tolerability of L-carnitine. The latter was assessed on the basis of laboratory test results [AST, ALT and creatine phosphokinase (CK) levels], spontaneously referred adverse events and premature treatment discontinuation due to adverse events.

The trial was approved by the Ethics Committee of all the involved hospitals and was conducted according to the Guidelines for Good Clinical Practice and the Declaration of Helsinki. All study participants gave their written informed consent.

This study was designed and supported by HELP Pharmaceuticals (a Hellenic pharmaceutical company). All agents (simvastatin, L-carnitine and placebo) were provided by the company. All blood samples were sent and measured at a central laboratory. The sponsor had no role in the interpretation of the data or writing of the manuscript.

Measurements

Anthropometric variables [body weight, height, body mass index (BMI), waist circumference], vital signs (blood pressure, heart rate), lipid profile (i.e. TC, LDL-C, HDL-C, TAG, Lp(a), apoA-I and apoB levels), serum creatinine, uric acid and TSH levels, plasma glucose and insulin levels, as well as the homeostasis model assessment (HOMA) index [HOMA index = fasting insulin (mU/L) × fasting glucose (mg/dL)/405] were assessed at baseline and 12 weeks. The estimated glomerular filtration rate (eGFR) was assessed by the Modification of Diet in Renal Disease (MDRD) equation. Because the Friedewald formula does not account for cholesterol associated with Lp(a), we also calculated LDL-C levels (mg/dL) corrected for Lp(a) concentration by the following equation: LDL-Ccor = LDL-C − [0.3 X Lp(a) (mg/dL)] [24].

All blood samples were drawn after a fasting period of at least 10 h, centrifuged at 3000 rpms for 15 min and immediately sent to the central laboratory at −20 °C (using dry ice packages).

Statistical Analysis

It was estimated that a sample size of 60 would give an 80% power to detect a 20% difference in the reduction of Lp(a) concentration between the 2 groups at a 2-sided alpha of 0.05.

The Kolmogorov–Smirnov test was used to evaluate whether each parameter followed a Gaussian distribution. All values are expressed as means ± standard deviations (SD) except for non-Gaussian distributed variables which are expressed as median (range). Differences in study parameters between baseline and post-treatment were evaluated by paired samples t test (or Wilcoxon's rank test for non-Gaussian variables). Independent samples t test (or Mann–Whitney test for parameters with non-Gaussian distribution) was used for between-group comparisons. Analysis of covariance (ANCOVA) adjusted for baseline values, was used for comparisons between treatment groups. Differences were considered to be significant at $p < 0.05$. All analyses were carried out with SAS statistical software version 9.1.3 (SAS Institute, Cary, North Carolina).

Results

We enrolled 58 patients (22 men and 36 women, mean age 56 ± 8 years). Baseline characteristics of study participants are shown in Tables 1 and 2. No significant difference in baseline demographic, clinical or laboratory parameters was found between the two groups. Furthermore, no significant change in demographic and clinical parameters was recorded during follow-up (data not shown). The compliance rate was >80% in all subjects.

After 12 weeks of treatment, plasma Lp(a) levels modestly decreased by 19.4% in the simvastatin/L-carnitine

Table 2 Serum metabolic parameters at baseline

	Simvastatin + L-carnitine ($n = 29$)	Simvastatin + placebo ($n = 29$)	p
Glucose (mg/dL)	109 ± 16	106 ± 15	NS
Insulin (mU/L)	12 (5.9–24.4)	14 (6.0–25.4)	NS
HOMA index	3.4 ± 0.8	3.7 ± 0.7	NS
e-GFR (mL/min/1.73 m^2)	73 ± 14	78 ± 11	NS
Uric acid (mg/dL)	5.0 ± 1.5	4.7 ± 1.0	NS
Total cholesterol (mg/dL)	292 ± 51	319 ± 59	NS
Triglycerides (mg/dL)	214 (150–362)	234 (150–401)	NS
High density lipoprotein cholesterol (mg/dL)	56 ± 13	63 ± 10	NS
Low density lipoprotein cholesterol (mg/dL)	195 ± 41	211 ± 46	NS
Lipoprotein (a) (mg/dL)	52 (20–171)	56 (26–108)	NS
Apolipoprotein A-I (mg/dL)	137 ± 19	142 ± 13	NS
Apolipoprotein B (mg/dL)	142 ± 32	144 ± 25	NS

Values are expressed as means ± SD except for insulin, triglycerides and Lp(a) which are expressed as median (range)

To convert values for glucose to mmol/L multiply by 0.05551. To convert values for insulin to pmol/L multiply by 7.175. To convert values for uric acid to μmol/L multiply by 59.5. To convert values for cholesterol to mmol/L multiply by 0.02586. To convert values for triglycerides to mmol/L multiply by 0.01129

HOMA homeostasis model assessment, *e-GFR* estimated glomerular filtration rate

group ($p = 0.01$), while a non-significant 6.7% reduction was observed in the simvastatin/placebo group ($p = 0.016$ for the comparison between groups) (Table 3; Figs. 1, 2). TC concentration was reduced by 26.1% in the simvastatin/L-carnitine group and 27.9% in the simvastatin/placebo group (both $p < 0.001$ *vs* baseline) with no difference between groups. Moreover, TAG were reduced by 28.3% in the simvastatin/L-carnitine group ($p = 0.0004$) and 26.2% in the simvastatin/placebo group ($p = 0.002$ compared with baseline) with again no difference between groups. Similar reductions were observed for LDL-C and apoB levels in both groups. Specifically, LDL-C decreased by 34.5% in the simvastatin/L-carnitine group and by 37.6% in the simvastatin/placebo group (both $p < 0.0001$ *vs* baseline), while the respective reductions in apoB levels were 33.8 and 34.2% (both $p < 0.0001$ *vs* baseline). Changes in LDL-Ccor were similar with those of measured LDL-C. HDL-C concentration remained unchanged with the combination treatment, while it was non-significantly reduced by 6.3% in the simvastatin/placebo group ($p = 0.062$). In contrast, apoA-I levels did not significantly change in any group (Table 3). There was no correlation between changes in Lp(a) and changes in LDL-C, TAG or apoB levels in any group (data not shown).

No changes were observed in anthropometric variables, plasma glucose and insulin levels, HOMA index, serum creatinine, uric acid, TSH levels and eGFR in either group (data not shown).

Safety

No elevations in liver transaminases >3 ULN or CK >5 ULN were observed in any patient. There were no differences in vital signs compared with baseline during the study. In addition, no adverse events were reported by any participant during the 12 weeks of treatment. All participants completed the study.

Discussion

We demonstrated a significant, though modest, reduction in Lp(a) levels with the combination of L-carnitine and simvastatin compared with simvastatin monotherapy in patients with mixed hyperlipidemia and elevated Lp(a) levels.

Several studies have assessed the efficacy of combined simvastatin/L-carnitine therapy *vs* simvastatin monotherapy on Lp(a) and other lipid and metabolic parameters, mainly in patients with type 2 diabetes mellitus (T2DM) [25–30].

In a study with a similar design but in diabetic patients, greater reductions in TAG, apoB and Lp(a) levels, as well as in glucose and HbA1c concentrations, were observed in the simvastatin/L-carnitine group compared with the simvastatin monotherapy group [25]. Furthermore, HDL-C increased in both groups, but significantly more in the combination treatment group. The significant changes in the

Table 3 Lipid profile at baseline and after 12 weeks of treatment

	Baseline*	12 weeks*	Percentage change
Total cholesterol (mg/dL)			
Simvastatin + L-carnitine	292 ± 51	216 ± 26.3	−26.1%[†]
Simvastatin + placebo	319 ± 59	230 ± 42.7	−27.9%[†]
Triglycerides (mg/dL)			
Simvastatin + L-carnitine	214 (150–362)	153 (90–265)	−28.3%[‡]
Simvastatin + placebo	234 (150–401)	173 (111–282)	−26.2%[¶]
High density lipoprotein cholesterol (mg/dL)			
Simvastatin + L-carnitine	56 ± 13	54 ± 7	0.0%
Simvastatin + placebo	63 ± 10	59 ± 7	−6.3%
Low density lipoprotein cholesterol (mg/dL)			
Simvastatin + L-carnitine	195 ± 41	128 ± 24	−34.5%[§§]
Simvastatin + placebo	211 ± 46	132 ± 37	−37.6%[§§]
Low density lipoprotein cholesterol corrected for Lp(a) levels (mg/dL)			
Simvastatin + L-carnitine	178 ± 29	114 ± 19	−36.0%[§§]
Simvastatin + placebo	194 ± 35	116 ± 31	−40.0%[§§]
Lipoprotein (a) (mg/dL)			
Simvastatin + L-carnitine	52 (20–171)	42 (15–102)	−19.4%[††, ¶¶]
Simvastatin + placebo	56 (26–108)	52 (27–93)	−6.7%
Apolipoprotein A-I (mg/dL)			
Simvastatin + L-carnitine	137 ± 19	129 ± 18	−6.0%
Simvastatin + placebo	142 ± 13	138 ± 8	−2.6%
Apolipoprotein B (mg/dL)			
Simvastatin + L-carnitine	142 ± 33	94 ± 22	−33.8%[§§]
Simvastatin + placebo	144 ± 25	95 ± 22	−34.2%[§§]

Values are expressed as means ± SD except for triglycerides and Lp(a) which are expressed as median (range)

To convert values for cholesterol to mmol/L multiply by 0.02586. To convert values for triglycerides to mmol/L multiply by 0.01129

[†] $p < 0.001$ *vs* baseline, [‡] $p = 0.0004$ *vs* baseline, [¶] $p = 0.0021$ *vs* baseline, [§] $p = 0.048$ *vs* baseline, [§§] $p = <0.0001$ *vs* baseline, [††] $p = 0.0105$ *vs* baseline, [¶¶] $p = 0.016$ between groups

parameters of glucose metabolism, as opposed to our study, may be due to the higher baseline levels of both parameters as the patients had overt DM. In this as well as in several other studies L-carnitine induced significant decreases in TAG levels. In fact, the TAG-lowering capacity of this agent was one of its first recognized properties [27], but has not been demonstrated in our as well as other studies [26, 29]. The reason for this difference is not clear; it is likely that the study population (i.e. baseline TAG levels, T2DM status, and sample size) plays a role.

In another study, diabetic patients ($N = 52$) with TAG <400 mg/dL and Lp(a) >20 mg/dL were randomized to simvastatin monotherapy (20 mg/day) or simvastatin (20 mg/day) plus L-carnitine (2 g/day) for 2 months [26]. Lp(a) levels increased in the simvastatin group but decreased by 13% in the combination treatment group ($p = 0.005$ for the comparison between groups) [26].

In an earlier study, patients with newly diagnosed T2DM (managed only with diet) and hypercholesterolemia ($N = 94$) were randomized to L-carnitine (1 gr bid) or placebo for 6 months [30]. Lp(a) levels decreased only in the L-carnitine group (−21%; $p < 0.01$ *vs* baseline, difference *vs* placebo −17%; $p < 0.05$) [30].

In a study involving patients with Lp(a) between 40 and 80 mg/dL, most of whom had high LDL-C and TAG levels, treatment with L-carnitine (2 g/day) was associated with a reduction in Lp(a) (−7.7% *vs* baseline and −11.7% *vs* placebo), with the decrease being more prominent in patients with higher baseline Lp(a) levels [29]. The population of this study resembles the one of ours; however, we demonstrated a greater reduction in Lp(a) with L-carnitine. In our study a more pronounced reduction of Lp(a) levels was noticed in patient(s) with the highest baseline levels in both groups (Figs. 1, 2). This may be related to the well-known regression to the mean effect.

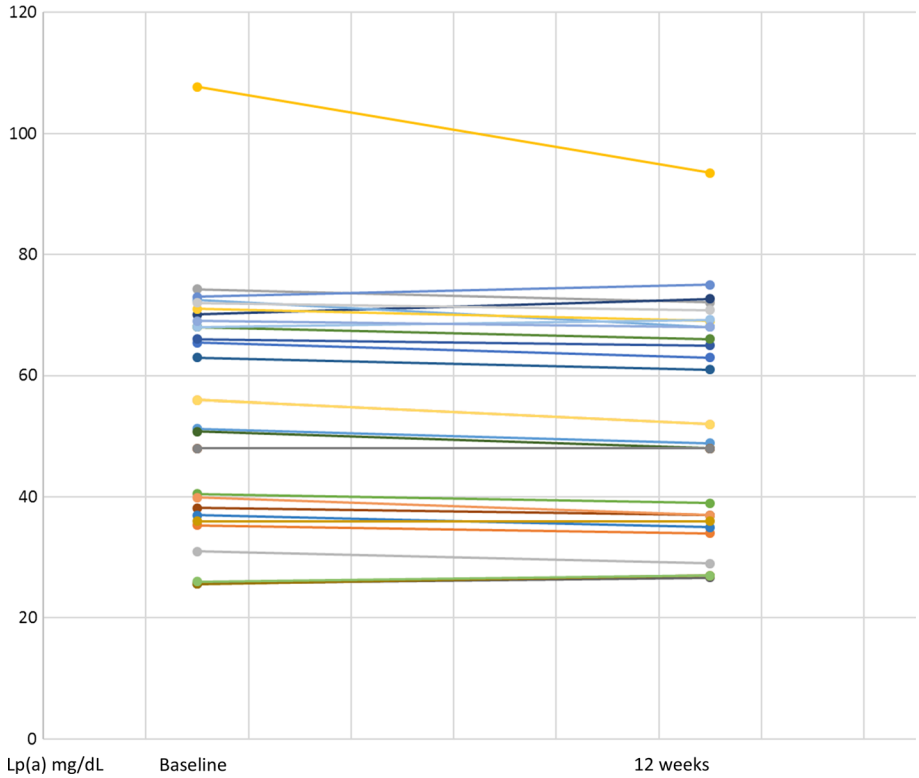

Fig. 1 Changes of Lp(a) levels in the simvastatin/placebo group

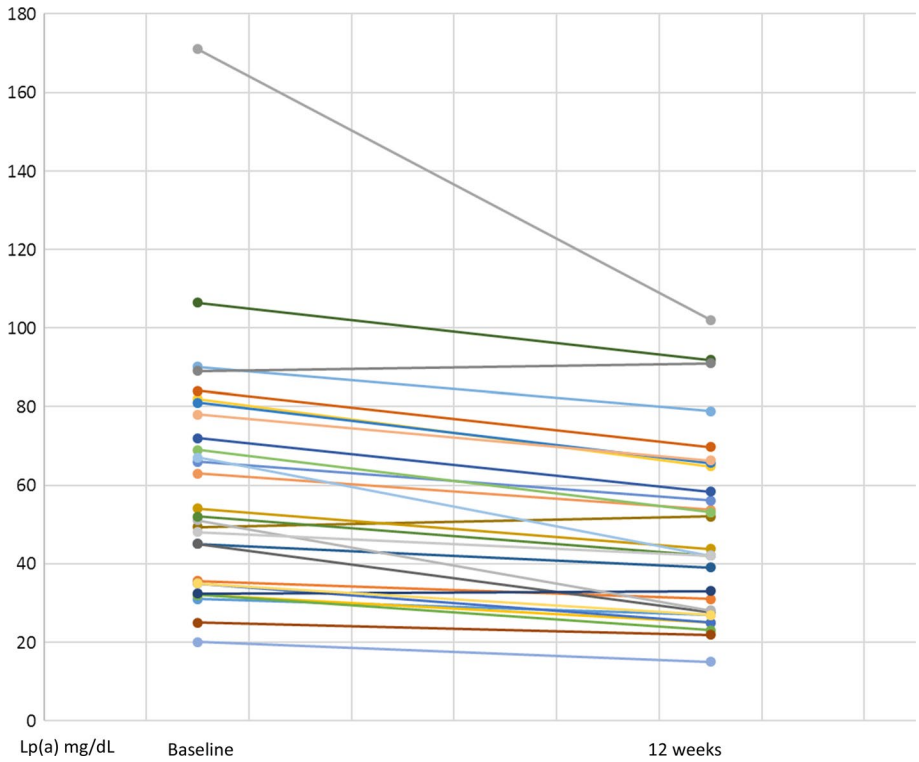

Fig. 2 Changes of Lp(a) levels in the simvastatin/L-carnitine group

In a study involving 32 diabetic patients with mixed hyperlipidemia (TC >200 mg/dL and TAG >150 mg/dL) randomized to simvastatin/L-carnitine or simvastatin monotherapy for 60 days, TAG were significantly reduced more in the combination treatment group ($p = 0.012$ for the comparison between groups) [28]. HDL-C levels were reduced in the

simvastatin monotherapy group, while they non-significantly increased with combination treatment [28]. The effect of treatment on Lp(a) was not assessed in this study.

Of interest are the different changes in HDL-C concentration in the various studies. Although simvastatin has been associated with HDL-C elevation of up to 12% [31], HDL-C concentration may drop with the introduction of statin treatment, which has been associated with increased CVD risk [32]. Changes in body weight, smoking pattern and physical activity may influence HDL-C concentration, but in the context of clinical trials these parameters do not differ significantly between groups. In our study body weight remained unchanged in both groups and, thus, may not have accounted for the reduction in HDL-C levels in the simvastatin/placebo group. Furthermore, the changes in TAG levels were similar in both groups and, thus, may not have affected HDL-C concentration. We may speculate that L-carnitine prevented a drop in HDL-C in the combination treatment group.

A recent meta-analysis assessing the impact of L-carnitine on plasma Lp(a) concentrations showed a significant reduction in Lp(a) levels following L-carnitine supplementation [23]. Of note, this reduction was significant with oral but not with intravenous L-carnitine administration. The results of the meta-regression analysis demonstrated that the pooled estimate was independent of L-carnitine dose and duration of treatment [23]. Furthermore, a significant decrease in plasma concentrations of TC and a borderline significant trend in LDL-C reduction were observed with L-carnitine therapy. In contrast, plasma HDL-C and TAG remained unaltered [23].

Apart from its effect on Lp(a) concentration, L-carnitine may have several other beneficial effects. Specifically, treatment with L-carnitine has been associated with improvement in insulin sensitivity and endothelial function [33], as well as reductions in oxidative stress and blood pressure [34]. Interestingly, in one study treatment with carnitine and simvastatin induced a reduction in the proportion of the highly atherogenic small-sized LDL particles and accordingly an increase in LDL particle size [35]. Furthermore, in a study including participants with non-alcoholic steatohepatitis L-carnitine administration resulted in significant reductions in HOMA index, liver enzymes, TC, LDL-C, TAG, glucose, C-reactive protein and tumor necrosis factor α levels, while it increased HDL-C concentration and improved histological scores [36]. Also, L-carnitine appears to be a safe and useful treatment option in patients with end-stage renal disease undergoing hemodialysis [37].

L-Carnitine is a trimethylated amino acid that is required for the transformation of free long-chain fatty acids into acylcarnitines and their subsequent transport into the mitochondrial matrix, where they undergo beta-oxidation for cellular energy production [38]. The exact mechanism responsible for L-carnitine lowering effects on Lp(a) is not completely understood. A possible pathway may be associated with the effects of L-carnitine on mitochondrial function. Defective mitochondrial function is a precursor event in several pathological conditions. The carnitine acyltransferase pathway is necessary for maintaining normal mitochondrial function. Excess levels of free fatty acids can induce mitochondrial dysfunction, resulting in cell death and/or enhanced secondary generation of reactive oxygen species. Treatment with L-carnitine can attenuate these effects [39]. Indeed, carnitine facilitates the transportation of fatty acids into mitochondria for their subsequent oxidation to generate adenosine triphosphate (ATP). As a result, by stimulating fatty acid break-down in mitochondria, L-carnitine may reduce liver production of Lp(a) [40].

The reduction in Lp(a) may be of clinical importance due to the atherogenic potential of this lipoprotein. In fact, Lp(a) may promote atherosclerosis via cholesterol deposition in the intima and enhancement of foam cell formation [14]. Lp(a) also appears to induce inflammatory cell recruitment and the binding of pro-inflammatory oxidized phospholipids to the vascular wall [41]. Furthermore, apo (a) may promote a prothrombotic state by inhibiting tissue factor pathway inhibitor as well as fibrinolysis [42].

Statins do not reduce Lp(a) levels consistently, while other drugs with favorable effects in Lp(a) lowering (e.g. niacin, estrogens) are limited due to adverse effects. Various drugs and nutraceuticals have been evaluated for their effect on lowering Lp(a) levels. Tibolone, a synthetic steroid, has been shown to significantly lower circulating Lp(a) levels in postmenopausal women [43]. On the other hand, a systematic review and meta-analysis of randomized controlled clinical trials showed that garlic supplementation did not change Lp(a) levels in the subgroup of trials lasting $\leq$12 weeks [44]. However, a significant elevation in plasma Lp(a) concentrations was found in trials lasting >12 weeks [44]. PCSK9 inhibitors may reduce Lp(a) up to 30% but are expensive [20]. Anti-sense anti-apo (a) drugs are effective (reductions of Lp(a) up to 80%) but are still in phase 1/2 [21]. In this context, the Lp(a) lowering effect of L-carnitine appears promising in terms of decreasing Lp(a) and possibly further reducing CVD risk [45].

On the other hand, gut microbial catabolism of L-carnitine can lead to the formation of trimethylamine (TMA) which is then converted in the liver into trimethylamine-*N*-oxide (TMAO) [46]. This transformation is mediated by two pathways: (1) the direct formation of TMA from L-carnitine by large intestine gut microbiota and (2) the catabolism of L-carnitine by small and large intestine gut microbiota to γ-butyrobetaine (γBB), which is then converted into TMA [46]. Of note, this transformation of L-carnitine to γBB, TMA and TMAO has been associated with progression of atherosclerosis [47–49]. However, a recent study has suggested that TMAO slows aortic lesion formation in a mouse

model and may have a protective effect against atherosclerosis development in humans [50]. Nevertheless, more data are warranted to clarify the exact role of L-carnitine and its derivatives in atherosclerosis development and progression.

In conclusion, it is evident that there is a large unmet clinical need. One-fifth of the population demonstrate large elevations of Lp(a) and thus cardiovascular risk, whereas we have very limited therapeutic options to effectively reduce Lp(a). In this study co-administration of L-carnitine with simvastatin was associated with significant reductions in Lp(a) compared with simvastatin monotherapy in subjects with mixed hyperlipidemia and elevated baseline Lp(a) levels. L-Carnitine might be a treatment option for Lp(a) lowering, while its pleiotropic properties may further promote CVD risk reduction. Prospective outcome trials will be required to fully elucidate the clinical value and safety of L-carnitine.

Strengths and Limitations of the Study

The major strengths of our study are its double-blind design and the use of a placebo arm. No patient dropped out during the study and the compliance was 80–100% in both treatment groups. Of note the majority of previous studies included diabetic patients. In fact, this is the first study to include patients with mixed dyslipidemia and elevated Lp(a) but without diabetes. On the other hand, this study assessed only metabolic parameters and not clinical outcomes. Furthermore, there was no L-carnitine monotherapy group as in clinical practice statin is always the basis of treatment. Also, it was not considered best practice to further delay statin treatment in these high CVD risk patients.

Compliance with Ethical Standards

Conflict of interest None.

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