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Effects of simvastatin and carnitine versus simvastatin on lipoprotein(a) and apoprotein(a) in type 2 diabetes mellitus

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Aim: The aim of the present study was to compare the effects of simvastatin and L-carnitine coadministration versus simvastatin monotherapy on lipid profile, lipoprotein(a) (Lp(a)) and apoprotein(a) (Apo(a)) levels in type II diabetic patients. *Patients/methods*: In this double-blind, randomized clinical trial, 75 patients were assigned to one of two treatment groups for 4 months. Group A received simvastatin monotherapy; group B received L-carnitine and simvastatin. The following variables were assessed at baseline, after washout and at 1, 2, 3 and 4 months of treatment: body mass index, fasting plasma glucose, glycated hemoglobin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, Apolipoprotein A1, Apo B, lipoprotein(a) and apoprotein(a). *Results*: At the end of treatment in the carnitine and simvastatin combined group compared with the simvastatin alone group, we observed a significant decrease in glycemia ($p < 0.001$), tryglicerides ($p < 0.001$), Apo B ($p < 0.05$), Lp(a) ($p < 0.05$), apo(a) ($p < 0.05$), while HDL significantly increased ($p < 0.05$). *Conclusions*: The coadministration of carnitine and simvastatin resulted in a significant reduction in Lp(a) and apo(a) and may represent a new therapeutic option in reducing plasma Lp(a) levels, LDL cholesterol and Apo B100.

Keywords: apoprotein(a), carnitine, lipoprotein(a), simvastatin, type 2 diabetes mellitus

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1. Introduction

Type II diabetes has emerged as a major health problem and tends to cluster with dyslipidemia in individuals at high risk of cardiovascular disease [1]. Although patients with type 2 diabetes have a high risk of death from cardiovascular disease (CVD) the traditional risk factors do not fully explain this excess of mortality. Lipoprotein(a) (Lp(a)) is a lipoprotein composed of apolipoprotein (a) (Apo(a)), which is covalently bound to low-density lipoprotein (LDL) via a single disulfide bond on apo B-100 [2-4]. Apo(a) is composed of unique loop structures called kringles, which are each stabilized by three disulfide bonds. In clinical studies, Lp(a) is recognized as a stronger cardiovascular risk factor in patients with highly elevated Lp(a) levels and those with additional risk factors [5,6]. Lp(a) has many potential atherogenic properties resulting from its LDL moiety. Apo(a) may confer proinflammatory, proatherogenic and prothrombotic properties. Apo B100 and apo(a) are expressed primarily in hepatocytes. Diet is not thought to influence Lp(a) values to any great extent. Nicotinic acid, tamoxifen, estrogens, progesterone and anabolic steroids might decrease Lp(a) concentrations [7-9]. Fibrates have been shown, in some studies, to reduce Lp(a)

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concentrations [10-12]. Nicotinic acid has a favorable effect on Lp(a) concentrations. However, this drug is difficult to tolerate at the high doses required. Fibric acid derivatives exert as favourable an effect on high-density lipoprotein (HDL) and triglyceride concentrations as well as on LDL quantity and quality. These drugs also reduce fibrinogen and possibly Lp(a) values [10,11]. Hormonal replacement therapy (HRT) in postmenopausal women is probably associated with a reduction in the risk of developing coronary artery disease [13,14]. Several, but not all, studies showed that thyroid replacement treatment decreases Lp(a) concentrations, probably because of an effect on apo(a) production, or possibly Lp(a) assembly. The activity of statin is controversial: some studies showed a decrease in Lp(a) levels, other studies underline that statins might increase Lp(a) concentrations [15-17]. Statins competitively inhibit 3-hydroxy-3-methyglutaryl (HMG)-CoA reductase, which catalyzes the conversion of HMG-CoA to L-mevalonate (L-MVLT), a key intermediate in cholesterol biosynthesis. The major effect of statins is a reduction in low-density lipoprotein cholesterol (LDL-C) concentrations, primarily mediated by inhibition of the rate-limiting step in cholesterol biosynthesis, resulting in an increase in LDL receptors in the liver [18]. In addition, statins can reduce triglycerides (TGs) and increase high-density lipoprotein cholesterol (HDL-C) [7], all of which lead to a reduced risk for coronary heart disease (CHD) in patients with type 2 diabetes mellitus [19,20]. L-carnitine is a natural constituent of higher organisms and in particular cells of animal origin [21]. L-carnitine covers an important role in lipid metabolism, acting as an obligatory cofactor for β-oxidation of fatty acids by facilitating the transport of long-chain fatty acids across the mitochondrial inner membrane as acylcarnitine esters. Furthermore, since carnitine behaves as a shuttle for acetyl groups from inside to outside the mitochondrial membrane, it covers also a key role in the glucose metabolism and assists in fuel sensing [22]. In a previous study, Sirtori *et al*. observed in patients with high Lp(a) levels treated with L-carnitine supplementation, a significant reduction in plasma Lp(a) levels [23]. In patients with type 2 diabetes mellitus after 3 and 6 months of L-carnitine treatment, Derosa *et al*. observed that L-carnitine significantly lowered the plasma Lp(a) level compared with placebo in selected hypercholesterolemic patients with newly diagnosed type 2 diabetes [24]. Finally in 52 patients with type 2 diabetes mellitus, Solfrizzi *et al*. demonstrated a significant decrease of Lp(a) levels in the simvastatin + L-carnitine group versus the simvastatin group [25]. The aim of the present study was to compare the effects of simvastatin and L-carnitine coadministration versus simvastatin monotherapy on lipid profile, lipoprotein(a) and apoprotein(a) levels in type 2 diabetic patients.

2. Patients and methods

Between January 2003 and 2006, outpatients with dyslipidemia and with type 2 diabetes mellitus that was managed through dietary restriction alone, attending the Department of Geriatrics, Catania University Hospital, Italy, were recruited for the study. After discontinuing all lipid-lowering drugs and supplements and/or treatment with other drugs known to affect mitochondrial metabolism, patients entered a 6-week dietary lead-in period.

Dietitians standardized breakfast, lunch and dinner, based on a diet prescribed to each patient. Each patient received 1400 – 1600 kcal/die: 55% carbohydrates, 25% proteins, 20% lipids (7% saturated), 105 mg cholesterol and 36 g fiber.

This controlled-energy diet was continued and the patients were instructed to maintain the same diet throughout the study.

After enrollment, patients provided a medical history and underwent a physical examination including body weight, blood pressure and pulse rate measurements with an ECG and a battery of biochemical/hematological tests for the measurement of lipids and other components that were part of the safety assessment. The trial has been previously approved by the Ethics Committee of the University of Catania. The trial was conducted according to the Guidelines for Good Clinical Practice and the Declaration of Helsinki.

3. Study design

Seventy-five patients entered this single-center, double-blind comparative study and assigned to one of two treatment groups for 4 months. This trial used a randomized design. After the washout period, the patients were randomly assigned to two treatment groups: group A (37 patients) received simvastatin monotherapy 20 mg tablet; group B (38 patients) received L-carnitine 2 g/day and simvastatin 20 mg.

Patients were seen by a dietitian every month; at each visit the dietitian provided instruction on dietary intake recording procedures as part of a behavior-modification program and the patients' resulting food diaries were later used for counseling.

The following variables were assessed at baseline, after washout and at 1, 2, 3 and 4 months of treatment: body mass index (BMI), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), total cholesterol (tot-C), LDL-C, HDL-C, TGs, apolipoprotein (apo) A1, Apo B, lipoprotein(a) and apoprotein(a).

3.1 Inclusion criteria

Patients aged 30 – 70 years with type 2 diabetes mellitus, according to the American Diabetes Association Criteria (American Diabetes Association Criteria, 2001), that was managed through dietary restriction alone, and with dyslipidemia (defined as LDL-C > 100 mg/dl, HDL-C < 40 mg/dl and/or tot-C > 200 mg/dl), according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), and Lp(a) levels > 20 mg/dl were enrolled.

Eligible patients provided written informed consent after receiving a full explanation of the study procedures.

3.2 Exclusion criteria

Patients with any of the following conditions were excluded from the study:

- history of hypersensitivity to HMG-CoA reductase inhibitors
- significant metabolic, renal, hepatic or gastrointestinal disease
- infection, gangrene or surgery within prior 3 months
- history of myocardial infarction, unstable angina or congestive heart failure
- history of alcoholism
- history of a convulsive disorder
- hyperuricemia
- history of acute peptic ulcer disease
- hypothyroidism or hyperthyroidism
- history of hormone use.

4. Clinical laboratory tests

Blood samples were obtained after the patients had fasted for 12 h overnight. Venous blood samples were taken from all patients between 0800 and 1000 h.

We used plasma obtained from the blood samples by the addition of EDTA and centrifugation at 3000 *g* for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C.

The FPGs were assayed with the glucose-oxidase method with intra- and interassay coefficients of variation (CVs) of 0.8% and 2.1% respectively.

The HbA1c level was measured with use of high-performance liquid chromatography with intra- and interassay CVs of 1.2% and 2.8% respectively.

The total cholesterol and triglycerides were determined using fully enzymatic techniques on a clinical chemistry analyzer; the intra- and interassay CVs were 1.1% and 2.2% respectively, for the total cholesterol measurement and 1.0% and 2.3% respectively for the triglycerides measurement.

The HDL-C level was measured after precipitation of plasma apo-B containing lipoproteins with phosphotungstic acid. The intra- and interassay CVs were 1.0% and 2.0% respectively. The LDL-C level was calculated using the Friedewald formula.

Apo A1 and Apo B were measured using immunoturbidimetric assays; the intra- and interassay CVs were 2.8% and 4.7% respectively.

Serum Lp(a) concentrations were measured in duplicate using a commercial ELISA (Immuno GMBH, Heidelberg, Germany). The intra- and interassay CVs were 4.6% and 8.2% respectively.

Apo(a) concentrations were measured in duplicate using a commercial ELISA (Mercodia Uppsala Sweden). The intra- and interassay CVs were 4.1% and 7.9% respectively.

All assays were carried out in our department laboratory.

4.1 Efficacy and tolerability assessment

Azotemia, creatininemia, hemocrome, liver enzymes, myoglobin, creatine phosphokinase (CPK) and urine were measured before the start of therapy (week 0) and at weeks 4, 8, 12 and 16 of treatment (study end).

Patients were advised to report unexplained muscle pain, low urine output, irritable bowel and any other adverse effects immediately, whether thought to be caused by the study drug or by cardiovascular problems.

5. Statistical analysis

Data were analyzed according to the 'intention to treat' principle. Patients' characteristics at randomization before the first treatment period were compared by means of a Student's *t* test. Descriptive statistics were prepared from the study sample and the results expressed as means ± standard deviation. Statistical significance in contingency tables was evaluated using chi-square and Fisher's exact tests. Student's *t* test for unpaired data, one-way ANOVA and Mann–Whitney rank sum test were used for comparisons of continuous variables. Statistical analysis was performed using tests for repeated measures as well as by controls for multiple comparisons with correction of Duncan procedure.

6. Results

Baseline clinical and demographic characteristics were similar between the two treatment groups (**Tables 1** and **2**).

6.1 Effects of simvastatin

After 16 weeks of simvastatin administration we observed a significant reduction of tot-C ($p < 0.001$), TGs ($p < 0.001$), LDL-C ($p < 0.001$), Apo A1 ($p < 0.001$) and Apo B ($p < 0.001$) and an increase of HDL-C ($p < 0.001$). Patients treated with simvastatin had no significant modifications in apo (a), apo A1 and in Lp(a) levels (**Table 3**)

6.2 Effects of simvastatin plus carnitine

After 16 weeks there was a significant reduction of tot-C ($p < 0.001$), triglycerides ($p < 0.001$), LDL-C ($p < 0.001$), Apo B ($p < 0.001$), glycemia ($p < 0.001$), HbA1c ($p < 0.001$), Lp(a) ($p < 0.05$) and apo (a) ($p < 0.05$). Moreover, there was a decrease in HDL-C ($p < 0.001$) (**Table 3**)

6.3 Comparison between groups

In the simvastatin plus carnitine treatment group versus the simvastatin group at the end of treatment we observed a decrease in glycemia (31.00 vs 9.00 mg/dl; $p < 0.001$), TGs (98.00 vs 35.00 mg/dl; $p < 0.001$), apo B (44.00 vs 17.00 mg/dl; $p < 0.05$), Lp(a) (9.30 vs 0.60 mg/dl; $p < 0.05$) and apo (a) (104.00 vs 2.00 U/L; $p < 0.05$) and an increase in HDL-C (4.90 vs 8.20 mg/dl; $p < 0.05$). Both treatments were well tolerated with no adverse events reported in either group (**Table 3**)

Table 1. Patients' clinical characteristics at baseline.

	Group 1	Group 2	P
Azotemia (mg/dl)	36 ± 0.7	37 ± 0.7	NS
Glycaemia (mg/dl)	136 ± 24	137 ± 20	NS
HbA1c (%)	7.0 ± 0.51	7.1 ± 0.48	NS
Creatininemia (mg/dl)	0.88 ± 0.36	0.86 ± 0.38	NS
Tot cholesterol (mg/dl)	259 ± 24	261 ± 21	NS
HDL cholesterol (mg/dl)	38.2 ± 0.7	38.4 ± 0.8	NS
Triglycerides (mg/dl)	298 ± 32	301 ± 24	NS
Lp(a) (mg/dl)	29.5 ± 10.8	29.7 ± 11.2	NS
LDL cholesterol (mg/dl)	161.4 ± 18.1	162.8 ± 16.4	NS
Apo A1 (mg/dl)	140 ± 18	146 ± 21	NS
Apo B (mg/dl)	166 ± 14	168 ± 15	NS

HbA1c: Glycated hemoglobin; Lp(a): Lipoprotein(a); NS: Not significant.

Table 2. Patient's demographic characteristics at baseline.

	Group 1	Group 2	P
Age (years)	51.4 ± 7.6	52.1 ± 8.1	NS
BMI	27.1 ± 2.4	27.8 ± 2.0	NS
HF	71 ± 16	75 ± 9	NS
SBP	150 ± 11	149 ± 12	NS
DBP	79 ± 12	80 ± 11	NS
Men/women	15/22	15/23	NS
Smokers/nonsmokers	20/17	20/18	NS

BMI: Body mass index; DBP: Diastolic blood pressure; HF: Heart frequency; NS: Not significant; SBP: Systolic blood pressure.

7. Discussion

This study demonstrates that the coadministration of carnitine with simvastatin significantly reduces plasma Lp(a) levels in type 2 diabetic patients. This reduction was related to the reduction in Apo B100, LDL-C and in apo(a).

Effective therapeutic modalities to reduce Lp(a) levels in humans are lacking. Lp(a) levels can be lowered by niacin, but niacin is associated with a high rate of severe flushing and glucose intolerance that limit its clinical use. In our study we observed changes in apo(a) concentrations parallel to those of Lp(a) concentrations. In a previous study, Cain *et al.* demonstrated that a large molar excess of apo(a) reduces the plasma clearance of Lp(a), which suggests that the apo(a) moiety plays a major role in mediating the plasma clearance and tissue uptake of Lp(a) [26]. Apo(a) is synthesized in hepatocytes and the rate of synthesis is related primarily to apo(a) gene transcription [27]. Post-translational regulation such as formation of the three disulfide bonds for each kringle type and N-linked glycation is important for proper apo(a) folding and transport out of endoplasmic reticulum. This process may take up to 120 min and depends on apo(a) size. Once apo(a) exits the endoplasmic reticulum, it travels to the Golgi apparatus, where it undergoes further post-translational modification and is finally transported to the hepatocyte cell surface. Lp(a) is then thought to the assembled from newly synthesized Apo B100, first by low affinity, noncovalent interactions between KIV-5 and KIV-8 and then through a disulfide bond between unpaired cysteine 4057 on KIV-9 on apo(a) and cysteine 4326 on the C-terminal region of Apo B100. Because small isoform apo(a) particles are more easily synthesized and secreted, it is postulated that subjects with small apo(a) isoforms have higher Lp(a) levels. Although apo(a) gene transcription contributes to plasma Lp(a) levels, some variability in those levels may be attributed to genetic polymorphisms of apo(a) [28,29]. It is also quite interesting that a modest inverse correlation is present between triglyceride levels and Lp(a)

Table 3. Mean values of examined parameters (SD) in two arms at the baseline, at weeks 4, 8, 12 and 16‡.

	Group A (simvastatin)					Group B (simvastatin + carnitine)				
	Baseline	**4 weeks**	**8 weeks**	**12 weeks**	**16 weeks**	**Baseline**	**4 weeks**	**8 weeks**	**12 weeks**	**16 weeks**
BMI (kg/m^2)	27.8 ± 2.4	27.5 ± 2.0	27.2 ± 1.9	27.1 ± 1.4	27.1 ± 1.2*	28.2 ± 2.5	27.4 ± 2.1	27.0 ± 2.2	26.8 ± 1.8	27.1 ± 1.9*
Glucose (mg/dl)	137 ± 28	135 ± 21	130 ± 22	130 ± 16	128 ± 16* ^{A}	136 ± 27	130 ± 22	118 ± 27	108 ± 24	105 ± 24*** ^{A}
HbA1c (%)	7.1 ± 0.8	7.1 ± 0.4	6.95 ± 0.6	6.7 ± 0.4	6.8 ± 0.7*	7.1 ± 0.4	7.0 ± 0.4	6.9 ± 0.5	6.7 ± 0.8	6.6 ± 0.8***
Total cholesterol (mg/dl)	251 ± 32	225 ± 28	200.1 ± 32	204 ± 28	201 ± 30***	256 ± 36	210 ± 32	200 ± 29	196 ± 31	190 ± 32***
HDL (mg/dl)	41.8 ± 3.8	44.2 ± 3.8	46 ± 4.1	46.1 ± 5.4	46.7 ± 5.7*** ^{B}	41.4 ± 3.7	45.1 ± 3.4	46.2 ± 3.1	49.1 ± 3.4	49.6 ± 3.8*** ^{B}
LDL (mg/dl)	157 ± 19	130.8 ± 17.1	107.9 ± 15.2	112.9 ± 18.1	109 ± 16.2***	159.4 ± 18.8	116.2 ± 24.2	111.8 ± 21.8	108.9 ± 18.2	105.1 ± 16.4***
Triglycerides (mg/dl)	265 ± 31	250 ± 31	231 ± 32	225 ± 37	230 ± 32*** ^{A}	278 ± 32	244 ± 31	210 ± 32	190 ± 33	180 ± 36*** ^{A}
ApoA1 (mg/dl)	147 ± 16	140 ± 16	138 ± 19	136 ± 21	138 ± 24* ^{C}	156 ± 26	136 ± 16	137 ± 15	138 ± 16	130 ± 16* ^{C}
ApoB (mg/dl)	161 ± 13	150 ± 12	144 ± 13	150 ± 16	144 ± 20*** ^{B}	174 ± 18	149 ± 18	150 ± 16	131 ± 20	130 ± 21*** ^{B}
Lp(a) (mg/dl)	30.4 ± 16	30.1 ± 15.7	30.0 ± 14.2	29.9 ± 15.8	29.8 ± 16.1* ^{B}	31.7 ± 15.4	29.4 ± 16.2	20.0 ± 13.1	18.2 ± 16.9	22.4 ± 15.7** ^{B}
Apo(a) (U/L)	282 ± 236	278 ± 225	279 ± 229	280 ± 210	275 ± 204* ^{B}	294 ± 270	253 ± 210	236 ± 200	196 ± 190	190 ± 167** ^{B}

Comparison within group A and within group B according to the values before the treatment: *NS, **$p < 0.05$; ***$p < 0.001$.

Comparison between groups A and B at the same phases of treatment: $^{A}p < 0.001$; $^{B}p < 0.05$; ^{C}NS.

‡All values are x± SD.

HbA1c: Glycated hemoglobin; HDL: High-density cholesterol lipoprotein; LDL: Low-density cholesterol lipoprotein; Lp(a): Lipoprotein(a); NS: Not significant.

levels, indicating that the rate of very low-density lipoprotein (VLDL) synthesis may affect Lp(a) metabolism [30]. In fact, up to 4% of apo(a) is present on VLDL particles, and these complexes may have a slower catabolism [31,32]. A study by Nassir *et al*. reported that apo(a) secretion from hepatoma cells may be linked to elements of cellular triglyceride assembly and secretion [33]. Optimizing body weight and tight glycemic control may beneficially influence Lp(a) values in patients with type 1 and type 2 diabetes. This effect is in part linked to triglyceride metabolism, which is impaired in type 2 diabetes, as well as the glycosylation of Lp(a), which interferes with its catabolism. In this setting, it has been shown that treating dyslipidemia in patients with diabetes improves the lipid profile and lowers the incidence of ischemic heart disease [22]. L-carnitine is reported to control hyperglycemia and improve insulin sensitivity [34] and also increase the peripheral glucose utilization in the insulin resistance patients [35]. The control action of carnitine in the synthesis of glycolitic and gluconeogenic key enzymes may have a beneficial effect in Lp(a) and in apo(a). L-carnitine plays an important role in the mitochondrial uptake of long-chain fatty acids by facilitating their transportation across the inner mitochondrial membrane to undergo β-oxidation and may reasonably reduce level fatty acid inflow for apo(a) production, thus distinctly lowering levels in the subjects presumably affected by excess production of this atherogenic lipoprotein. Combined treatment with simvastatin and L-carnitine may have not only accelerated the utilization of intracellular fatty acids by improving fatty acid oxidation capacity but may also have inhibited the influx of long-chain fatty acid by decreasing serum TGs [36]. The decrease in serum TGs is correlated with an increase in HDL-C. Consistent evidence from the literature demonstrates that there is a strong correlation between Apo A1 and HDL-C levels [37,38]. In our study we observed that Apo A1 concentrations decrease after treatment, whereas HDL-C levels increase. The activity of our treatment may be independent in Apo A1 concentration and HDL cholesterol. Other studies have reported individuals with familiar hypercholesterolemia, in which there is a genetic absence of functional LDL receptors (LDL-Rs) having increased plasma Lp(a) levels, suggesting a role for LDL-Rs and the liver in the plasma clearance of Lp(a) [39]. Several receptors that mediate the binding and uptake of lipoproteins containing Apo B100 have been proposed as receptors for Lp(a) metabolism. These include the LDL-Rs, megalin/gp330, the LDL-R-related protein and the VLDL receptor [40-42]. It has been suggested that other members of the LDL-R family participate in Lp(a) catabolism. It has been shown that the VLDL receptor mediates the uptake and catabolism of Lp(a) in fibroblasts expressing the VLDL receptors and that this uptake is mediated by apo(a) [43]. Keesler *et al*. identified on apo(a) receptor that mediates the binding and internalization of apo(a) and Lp(a) in cholesterol-loaded macrophages [44]. The preponderance of evidence indicates that the LDL receptor does not play a major role in Lp(a) clearance [27]. Approximately 10 – 25% of Lp(a) is converted to LDL when apo(a) is cleaved off and LDL is then cleared by the LDL receptor. Limitations of the study included that we did not compare the two study groups with a carnitine monotherapy group. We chose to compare carnitine + simvastatin versus simvastatin alone because statins are the cornerstone in the management of dyslipidemia. Future research could include studies on mono- versus combination therapy to ascertain whether the significances between mono- and combination therapies are due to a pure additive effect of carnitine or a synergistic effect. In conclusion, the coadministration of carnitine and simvastatin resulted in a significant reduction in Lp(a) and apo(a) and may represent a novel therapeutic option in reducing plasma Lp(a) levels, LDL-C and Apo B100 [36].

Declaration of interest

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