Acta Pædiatrica, 2005; 94: 711–716

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The effect of oral L-carnitine supplementation on the lipid profiles of hyperlipidaemic children

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Abstract

Aim: To investigate the carnitine status and the effect of carnitine supplementation on serum lipid profiles in children with hyperlipoproteinaemia, a clinical open trial was conducted at Hacettepe University Ihsan Dogramaci Children's Hospital, Section of Nutrition and Metabolism. *Methods:* Patients were given carnitine at a dose of 100 mg/kg/d for 12 wk. Blood samples for the determination of lipid profile and carnitine levels and urine samples for carnitine levels were obtained on admission, at week 4 and week 12 of the study period. *Results:* A total of 41 children were enrolled in the study: 20 patients had type II heterozygotes, eight patients had type II homozygotes, three patients had type III, six patients had type V and four patients had secondary hyperlipidaemias. Serum and urine carnitine levels were within normal limits on admission. No significant correlations were found between serum carnitine levels and serum lipid profiles. Serum HDL and apolipoprotein A-I decreased significantly during the 12 wk of intervention in type II heterozygotes. In type II homozygotes, total cholesterol and LDL levels at weeks 4 and 12 increased significantly compared to initial levels. No significant change was noted for lipid parameters in hyperlipoproteinaemia type V.

Conclusion: The results of this trial demonstrated that carnitine supplementation was of no benefit for children with hyperlipidaemias, especially in primary hyperlipoproteinaemia type II heterozygotes, homozygotes and type V.

Key Words: *Carnitine, children, hyperlipoproteinaemia, supplementation*

Introduction

Carnitine is essential for the transport of fatty acids from cytosol into the mitochondria and optimal mitochondrial β-oxidation of long-chain fatty acids. The reduction of carnitine levels in tissues results in a partial oxidation of fatty acids [1]. Because of its role in fatty acid metabolism, carnitine has been considered as a therapeutic agent in the treatment of hyperlipidaemia. Additionally, experimental studies in hyperlipidaemic rabbits showed that L-carnitine treatment significantly reduced blood levels of very low density lipoprotein (VLDL) cholesterol, VLDL triglycerides and had no effect on high density lipoprotein (HDL) cholesterol [2,3]. Interestingly, Sayed-Ahmed et al. [4] reported that endogenous carnitine depletion might be an additional risk factor in atherogenesis and that carnitine supplementation prevented the progression of atherosclerotic lesions.

In hyperlipidaemic patients, coronary disease, cerebrovascular events and sudden death at early adult ages are common. There is strong evidence to suggest that the pathological changes, including coronary lipid lines and fibrous plaques, occur during childhood [5]. In this way, high blood cholesterol levels in children play an integral role in the development and progression of coronary heart disease in later life [6,7]. For this reason, management studies in children with hyperlipoproteinaemia (HLP) become more important. There are different drug options for the treatment of hyperlipidaemic patients, but still there is no ideal therapy for HLP. Due to the high morbidity and mortality of the disease, the difficulty and necessity of life-long compliance with diet and drug treatment, and side effects of antilipidaemic drugs, new treatment modalities including garlic, soy protein, nuts and carnitine have been under research [7–9]. The effect of carnitine on lipid metabolism as well as its tolerance are the basis for clinical use of this substance for lipid-lowering treatment.

Some studies in uraemic patients indicated that L-carnitine lowered serum cholesterol, triglycerides

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(Received 21 April 2004; revised 16 November 2004; accepted 18 November 2004)

ISSN 0803-5253 print/ISSN 1651-2227 online
DOI: 10.1080/08035250510027273

and free fatty acids, and increased β-hydroxybutyrate and HDL cholesterol [10–13]; yet, in other studies, carnitine was found to be without effect on lipid metabolism [14,15]. In addition, trials performed to study the effect of L-carnitine supplementation in adult patients with primary HLP showed some improvement in lipid parameters [16–19]. However, to date, the effect of carnitine supplementation has not been investigated in children with HLP. Therefore, this study was carried out in order to evaluate the carnitine status and the effect of carnitine supplementation on serum lipid profiles in children with HLP.

Material and methods

An open clinical trial was conducted in children with HLP at Hacettepe University.Ihsan Dogramaci Children's Hospital, Section of Nutrition and Metabolism, between November 2002 and April 2003. The exclusion criteria were treatment with lipid-lowering drugs 30 d before the study, other concomitant drug treatments that might interfere with lipid and lipoprotein metabolism (beta-blockers, steroids, thiazide diuretics, benzodiazepines, clonidine, cimetidine, heparin, thyroid hormones, phenylhydantoine) and those with primary carnitine deficiency. This study was approved by the Ethical Committee for Medical, Surgical and Drug Research at Hacettepe University Faculty of Medicine, Ankara, Turkey (10.10.2002, LUT 02/47).

Before enrolment, children and their families were given a full explanation of the study, and written informed consent was obtained. All participating cases were on therapeutic diet, and the diet was continued throughout the study. A standard history was taken, and physical examination was performed initially on admission. Data included age, weight, height, age at diagnosis and type of HLP. Serum samples for lipid profiles and blood carnitine levels and urine samples for carnitine levels were obtained on admission. Blood samples were collected after 12 h of fasting. While the optimal dose of carnitine has yet to be determined, doses of 2–3 g/d have been given in adults with primary HLP [17–19]. Considering these studies, the amount of carnitine to be given as supplement was decided as 100 mg/kg/d, divided into two doses per day, with a maximum of 2 g/d (L-carnitine capsule 500 mg® GNC [General Nutrition Corp], Pittsburgh, USA). During the intervention period, subjects were followed up for any adverse effect including changes in eating habits, diarrhoea and fishy odour. Patients were also examined at week 4 and week 12 of the study period. At each visit, fasting blood samples and urine samples were obtained. Side effects were assessed by a questionnaire at each visit.

Fasting blood samples were obtained at each visit for serum lipid profiles and blood carnitine levels. Serum samples were analysed within 4 h of sampling for serum lipid profiles. Serum triglycerides, total cholesterol and HDL-C were analysed by enzymatic colorimetric test (Boehringer Mannheim Kits, Germany) with Roche Modular Analytics (Roche Diagnostics Corporation, Indianapolis, IN, USA) as described previously [20,21], and LDL was calculated as total cholesterol–HDL–triglyceride/5. VLDL was calculated as triglyceride/5 [22]. Serum apo A-I, apo B and Lp(a) were determined by the turbidity immunoassay method using the Beckman Coulter Image Immunochemistry System (Miami, USA) [23]. For all measurements in our laboratory, the coefficients of interassay and intra-assay variation were less than 5.0%, and blinded quality-control specimens were included in each assay. Analyses were conducted at the Hacettepe University Routine Biochemistry Laboratory, under regular quality control procedures including the use of reference pools and blinded duplicate samples.

Urine and blood samples were spotted on a Guthrie card. These samples were stored at +4°C until analysed. Free carnitine and acylcarnitine were measured from dried filter paper blood and urine spots using electrospray tandem mass spectrometry (Micromass, Manchester, UK) as previously described [24,25].

For statistical analysis, SPSS 11.5 for Windows was used. Cases were classified [8]. Due to the limited number of patients in groups other than the type II heterozygote hyperlipidaemia group, comparisons among groups were not done. During the intervention period, the changes in the proportions of cases with abnormal lipid profiles were compared with the χ^2 (McNemar) test. The normality of data distribution was checked using the Kolmogorov-Smirnov test in the whole group and the subgroups.

In the whole group and the type II heterozygote hyperlipidaemia group, a repeated-measures ANOVA was conducted on parameters to examine the time effect of intervention with simple comparison. The mean and standard deviation of the parameters were calculated. Mean differences between follow-up parameters were given. Serum VLDL and Lp(a) data were log-transformed for the analysis and presented as the geometric means and minimum–maximum, because the distributions of the raw data values were skewed in the type II heterozygote hyperlipidaemia group.

In cases with type II homozygotes and type V hyperlipidaemia (6–8 cases in the group), Freidman analysis was used to test the time effect of intervention. When interaction was found to be significant, a *post hoc* test was undertaken, which compares the differences in average ranks for all possible pairs, to determine where the differences lie [26]. The results were given as the median and interquartile range. Due to a limited number of cases with type III and secondary

Table I. General characteristics of hyperlipoproteinaemia cases.

	Type II heterozygotes	Type II homozygotes	Type III	Type V	Secondary type
n	20	8	3	6	4
Male sex	11 (55%)	3 (37.5%)	1 (33.3%)	5 (83.3%)	0 (0%)
Present age, y	10.3±4	8±3.6	12.8±0.9	8.4±4.2	13.7±7.8
Age at diagnosis, y	9.1±3.7	4.8±2.1	9.7±1.7	1.9±2.9	12.6±7.3
Follow-up period, y	1.2±1.5	3.3±2.5	3.0±0.8	6.5±5.8	1.1±1.1
Positive family history	19 (95%)	8 (100%)	2 (66.7%)	0 (0%)	1 (25%)
Presence of xantomas	0 (0%)	5 (62.5%)	0 (0%)	0 (0%)	0 (0%)
Weight, kg	37.3±14.9	22.6±8.6	50.3±19.7	26.1±10.9	37.9±26.4
Height, m	137±22.1	119.6±20.8	148.7±9.3	124.6±19.6	124.9±36.9
BMI, kg/m^2	19.1±3.7	15.2±1.2	22.3±6.9	16.2±1.4	21.4±8.5
BMI >95th percentile	6 (30%)		1 (33.3%)		1 (25%)

hyperlipidaemias, changes in lipid profile over the course of carnitine supplementation were not analysed statistically.

Results

A total of 41 children were enrolled in the study: 20 patients had HLP type II heterozygotes, eight patients had type II homozygotes, three patients had type III, six patients had type V and four patients (hypothyroidism, yellow nail syndrome, Down syndrome, Turner syndrome) had secondary hyperlipidaemias. The mean age was 10.1 y (SD 4.4, range 13 mo–18 y). Of 41 patients, 20 (48.8%) were male. Subject characteristics are given in Table I. Eight patients (19.5%) had BMI higher than the 95th percentile. There was no case with low serum and urine carnitine levels on admission. No significant correlations were found between blood carnitine levels and serum lipid profiles on admission. Compliance with the supplement was excellent in all subjects and based on the returned tablets and urinary carnitine levels (Table II). No side effects due to carnitine supplementation were encountered in our patients.

In comparison with baseline values, HDL levels decreased by 2.1% at week 4 ($p>0.05$) and by 12.0% at week 12 ($p<0.05$). The reductions in apo A-I were 6.7% and 4.9% at weeks 4 and 12, respectively. The changes in this ratio were statistically significant at every time point ($p<0.05$). In comparison with the baseline, the cholesterol/HDL ratio increased significantly, by 18.3% at week 4 and 25.4% at week 12 ($p<0.05$). No significant changes were seen in other lipid parameters during the trial. A low HDL level (0.91 mmol/l or less) was recorded in 40.5% of patients on admission and 54.8% of patients after 12 wk of therapy, and this was found to be statistically significant. No significant change in the frequency of pathological levels was noted for other lipid parameters.

Table II. Serum lipid profiles and blood and urinary carnitine levels following intervention periods in hyperlipoproteinaemia type II heterozygotes.

	Week			
Characteristics[a]	0	4	12	*p*
Cholesterol, mmol/l	6.65±1.20	6.59±1.65	6.70±1.44	n.s.
Triglyceride, g/l	0.92±0.34	1.08±0.46	1.16±0.57	n.s.
HDL, mmol/l	1.35±0.36	1.22±0.30	1.14±0.31[d]	0.029
LDL, mmol/l	4.87±1.16	4.81±1.58	4.96±1.37	n.s.
VLDL, g/l[b]	0.199 (0.09–2.06)	0.198 (0.10–0.41)	0.209 (0.10–0.49)	n.s.
Apo A-I, g/l	1.42±0.18	1.35±0.21[c]	1.30±0.17[d]	0.002
Apo B, g/l	1.18±0.23	1.17±0.30	1.22±0.27	n.s.
Lp(a), μg/ml[b]	251 (105–1680)	267 (105–1680)	300 (34–1680)	n.s.
Blood free carnitine, μmol/l	26.92±5.88	31.63±6.81	30.22±10.19	n.s.
Blood acylcarnitine, μmol/l	14.03±3.64	15.08±2.87	14.85±4.27	n.s.
Urine free carnitine, μmol/l	42.1±47.9	409.4±453.7[c]	480.4±365.2[d]	0.001
Urine acylcarnitine, μmol/l	12.8±7.7	26.7±12.3[c]	28.2±8.3[d]	0.001

[a] Mean±SD; [b] GMT (min.–max.); [c] comparison between week 4 and baseline; [d] comparison between week 12 and baseline.
HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; apo A-I: apolipoprotein A-I; apo B: apolipoprotein B; Lp(a): lipoprotein(a); n.s.: not significant.

Table III. Serum lipid profiles and blood and urinary carnitine levels following intervention periods in hyperlipoproteinaemia type II homozygotes and type V.

Characteristics[a]	HLP type II homozygotes ($n=8$)				HLP type V ($n=6$)			
Week	0	4	12	p	0	4	12	p
Cholesterol, mmol/l	15.02 (13.04–20.13)	18.30 (17.04–21.24)[b]	17.04 (15.74–19.50)[c]	0.06	4.53 (3.23–6.11)	5.30 (3.33–7.94)	5.18 (3.83–5.55)	n.s.
Triglyceride, g/l	1.19 (1.05–1.62)	1.52 (0.89–1.80)	1.39 (1.27–1.53)	n.s.	12.22 (6.61–14.59)	10.73 (6.39–17.03)	12.17 (8.63–14.96)	n.s.
HDL, mmol/l	0.83 (0.63–0.93)	0.63 (0.46–0.69)	0.60 (0.54–0.70)	n.s.	0.48 (0.43–0.69)	0.70 (0.27–1.15)	0.56 (0.31–0.71)	n.s.
LDL, mmol/l	13.64 (11.47–18.87)	16.65 (15.73–19.85)[b]	15.63 (14.49–18.24)[c]	0.02	2.64 (1.37–4.45)	2.62 (1.06–3.56)	2.20 (1.57–3.02)	n.s.
VLDL, g/l	0.24 (0.21–0.32)	0.30 (0.18–0.36)	0.28 (0.25–0.31)	n.s.	2.45 (1.08–2.92)	2.14 (0.59–3.41)	2.44 (1.73–2.99)	n.s.
Apo A-I, g/l	0.84 (0.63–0.95)	0.66 (0.60–0.70)	0.65 (0.58–0.71)	n.s.	0.82 (0.73–0.91)	0.90 (0.60–1.09)	0.84 (0.73–1.15)	n.s.
Apo B, g/l	3.00 (2.79–3.82)	3.63 (3.13–3.94)	3.55 (2.80–3.94)	n.s.	0.91 (0.66–1.46)	1.16 (0.86–3.94)	0.92 (0.80–1.68)	n.s.
Lp(a), μg/ml	109 (105–1004)	136 (105–1136)	122 (105–1680)	n.s.	105 (105–105)	105 (105–105)	105 (105–105)	n.s.

[a] Median (interquartile range); [b] comparison between week 4 and baseline; [c] comparison between week 12 and baseline.
Abbreviations: see Table I.

When analysis was done in HLP type II heterozygote patients, HDL levels at weeks 4 and 12 were reduced by an average of 6.9% and 12.1%, respectively, as compared to the initial levels. In comparison with baseline values, serum HDL levels decreased significantly at week 12 (1.35 ± 0.36 and 1.14 ± 0.31 mmol/l, respectively, $p<0.05$, Table II). Apo A-I levels at weeks 4 and 12 compared to initial levels were reduced by an average of 5.1% and 8.3%, respectively ($p<0.05$). No significant changes were seen in serum total cholesterol, triglyceride, LDL, VLDL or Lp(a) concentrations during the trial (Table II). In comparison with the baseline, the cholesterol/HDL ratio increased by 10.9% at week 4 ($p>0.05$) and 23.0% at week 12 ($p<0.05$).

In HLP type II homozygote patients, total cholesterol and LDL levels at weeks 4 and 12 increased significantly compared to initial levels ($p<0.05$, Table III). No significant change was noted for lipid parameters in type V HLP.

Urine free carnitine and acylcarnitine levels were increased compared to initial levels with intervention in HLP type II heterozygotes (Table II), type II homozygotes and type V.

Discussion

The most important effect expected from an antilipidaemic drug is the reduction of LDL along with a rise in HDL. However, in this study, serum HDL cholesterol and apo A-I decreased significantly during week 12 of the intervention, and the cholesterol/HDL ratio increased in cases with HLP type II heterozygotes. In HLP type II homozygotes, total cholesterol and LDL levels increased significantly during the intervention period. Contrary to the results in the present study, Pola et al. [17] found that carnitine treatment (3 g/d for 40 d) in HLP type II heterozygotes ($n=16$) aged between 35 and 70 y reduced cholesterol levels by 27.2% and the cholesterol/HDL ratio by 32.5%, and increased lipoprotein α levels by 30.7% ($p<0.05$). Similarly, Sirtari et al. [18] examined the effect of carnitine supplementation (2 g/d for 12 wk) on 36 young adults with high Lp(a) values in a placebo-controlled study, and they found that the Lp(a) values compared to initial values and those of the placebo group reduced by 7.7 and 11.7%, respectively ($p<0.05$); in those given placebo, no significant changes were observed. These controversial results of carnitine supplementation in HLP patients remain to be explained. In previous studies, carnitine dosage (2–3 g/d) and the duration of treatment are similar to the present one (100 mg/kg/d carnitine, max. 2 g/d) [17,18]. In fact, it has been reported that, in patients receiving high dosages of carnitine supplementation, even an increase in serum triglycerides may be found due to carnitine-dependent shuttling of acetyl groups

to the cytosol, where they can be used for fatty acid resynthesis and in the liver for subsequent triglyceride and VLDL synthesis [10,27,28]. On the other hand, a decrease in plasma triglycerides was reported in patients unresponsive to 20 mg/kg of L-carnitine when dosage was increased to 60 mg/kg [13]. It was reported that the hypolipidaemic effect of carnitine may take a long time to appear in hyperlipidaemic patients [28]. However, a 3-mo supplementation in the present study was sufficient to show a change in serum lipid parameters.

Another possible explanation for controversial results is that the effect of carnitine supplementation might change with age. All the former carnitine studies on its use as a hypolipidaemic agent were on adult patients.

In addition, the disparate results concerning the effect of carnitine on serum lipid profile may be partly related to the HLP type, and the primary defect causing hyperlipidaemia might affect the response to carnitine treatment. Contrary to the previous studies done in adult HLP cases (HLP type IV and HLP type II heterozygotes) and uraemic patients [10,16–19], no changes in serum lipid parameters were detected in cases with HLP type V, and a lipaemic effect was seen in cases with HLP type II heterozygotes and homozygotes following carnitine supplementation in the present study.

It should also be mentioned that other factors, such as long-term treatment compliance, variation in patient selection, lipid status, dietary patterns, presence or absence of drugs affecting lipids, and individual response to the drug, could also be responsible for the inconsistent results observed in the literature. High urinary excretion of carnitine at week 4 and week 12 may indicate a good compliance of the patients with supplementation in this study. Additionally, serum carnitine levels might affect carnitine response on lipid metabolism. However, all the patients in the present study had normal serum and urine carnitine levels on admission. Elisaf et al. [10] found that the beneficial effect of L-carnitine administration on serum triglycerides was more evident in patients with baseline hypertriglyceridaemia in hypertriglyceridaemic haemodialysis patients. Vacha et al. [13] reported that carnitine reduced triglyceride levels only in cases with high basal triglyceride levels and low levels of HDL and apo A; however, no changes were detected in the lipid parameters of cases with high basal triglyceride values and normal HDL and apo A. In the present study, a limited number of cases had high basal triglyceride levels with low HDL levels ($n = 12$), and no changes in serum lipid profiles were detected with carnitine supplementation. Therefore, the lipid status of cases might affect the individual response to carnitine supplementation. In addition, it has been postulated that an individual's genetic background could also determine responsiveness to nutritional therapy and/or diet-related disease progression [29].

In conclusion, the present trial has demonstrated that carnitine supplementation has no beneficial effect on the lipid profiles of childhood hyperlipidaemias, especially in primary HLP type II homozygotes, heterozygotes and type V. Therefore, carnitine supplementation should not be recommended as a therapeutic agent in cases with childhood hyperlipidaemia.

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