L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial[1–3]

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ABSTRACT

Background: Centenarians are characterized by weakness, decreasing mental health, impaired mobility, and poor endurance. L-Carnitine is an important contributor to cellular energy metabolism.

Objective: This study evaluated the efficacy of L-carnitine on physical and mental fatigue and on cognitive functions of centenarians.

Design: This was a placebo-controlled, randomized, double-blind, 2-phase study. Sixty-six centenarians with onset of fatigue after even slight physical activity were recruited to the study. The 2 groups received either 2 g levocarnitine once daily ($n = 32$) or placebo ($n = 34$). Efficacy measures included changes in total fat mass, total muscle mass, serum triacylglycerol, total cholesterol, HDL cholesterol, LDL cholesterol, Mini-Mental State Examination (MMSE), Activities of Daily Living, and a 6-min walking corridor test.

Results: At the end of the study period, the levocarnitine-treated centenarians, compared with the placebo group, showed significant improvements in the following markers: total fat mass (−1.80 compared with 0.6 kg; $P < 0.01$), total muscle mass (3.80 compared with 0.8 kg; $P < 0.01$), plasma concentrations of total carnitine (12.60 compared with −1.70 μmol; $P < 0.05$), plasma long-chain acylcarnitine (1.50 compared with −0.1 μmol; $P < 0.001$), and plasma short-chain acylcarnitine (6.0 compared with −1.50 μmol; $P < 0.001$). Significant differences were also found in physical fatigue (−4.10 compared with −1.10; $P < 0.01$), mental fatigue (−2.70 compared with 0.30; $P < 0.001$), fatigue severity (−23.60 compared with 1.90; $P < 0.001$), and MMSE (4.1 compared with 0.6; $P < 0.001$).

Conclusions: Our study indicates that oral administration of levocarnitine produces a reduction of total fat mass, increases total muscular mass, and facilitates an increased capacity for physical and cognitive activity by reducing fatigue and improving cognitive functions. *Am J Clin Nutr* 2007;86:1738–44.

KEY WORDS L-Carnitine, L-acetyl-carnitine, centenarians, fatigue, cognitive functions

INTRODUCTION

Aging is characterized by a slow decline of the physiologic functions, with a progressive deterioration of various organs and consequently of the organism until death, and appears to be associated with a substantial loss of the ability to regulate energy balance (1, 2). Mitochondria, because of their critical importance for energy production, have attracted the attention of scientists interested in unraveling the complex changes associated with aging and age-related diseases (3, 4). Because mitochondria are responsible for most cellular energy conversion, these associations are consistent with the hypothesis that DNA damage in mitochondria may contribute to the age-associated decrease in energy expenditure for physical activity (5).

L-Carnitine is an endogenous molecule and is an important contributor to cellular energy metabolism. It is present ubiquitously in the organism, and the main concentrations are found in the most active metabolic tissue, such as the myocardium and skeletal muscle. L-Carnitine is indispensable for the transport of long-chain fatty acids across the inner mitochondrial membrane to their site of oxidation and the production of energy in the form of ATP (6, 7). Among all the substances whose concentration decreases with age, L-carnitine diminution is fundamentally important, given its function in the production of energy. One of the most important consequences of carnitine deficiency is therefore manifested in the alteration of the metabolic pathways that lead to the production of energy.

In our previous study, the treatment with exogenous levocarnitine in elderly subjects showed a progressive increase in total muscle mass and a significant reduction in muscle fatigue compared with placebo (8). In the elderly variations are found in the plasma concentration of L-carnitine even if its causes are not known. In fact, the concentration of carnitine actually increases with the advancement of age until ≈70 y, subsequently tending to diminish the parallel in the reduction in body mass index (in kg/m^2) and muscle mass (9). The aim of this study was to evaluate the efficacy of L-carnitine in physical and mental fatigue and on the cognitive functions of centenarians.

SUBJECTS AND METHODS

Subjects

A total of 70 centenarians, aged from 100 to 106 y (24 men, 46 women) were recruited to the study. The centenarians were treated with L-carnitine for 6 mo.

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Wessely's test and Powell's test were used to examine fatigue, both mental and physical, and the severity was expressed with the Krupp's test. The Wessely and Powell score consists of 2 scales measuring physical fatigue [8 items scored from 0 (no fatigue) to 2 (highest possible fatigue); total score range: 0–16] and mental fatigue (5 items; total score range: 0–16) (10). We also used the Fatigue Severity Scale, composed of 9 items (11). Here, the total score ranges from 9 to 63 and is directly related to the severity observed. Mini-Mental State Examination (MMSE) was used to assess cognitive function (12, 13, 14). The MMSE score ranges between 0 and 30.

Subjects were excluded if they had experienced any of the following: a significant medical or surgical event within the previous 3 mo, significant cardiac failure (New York Heart Association class III or IV) (15), acute or chronic renal failure, severe respiratory disorders, severe digestive disorders, severe cognitive disorders, diabetes mellitus, or other endocrine diseases. Patients taking corticosteroids or diuretics were also excluded from the trial.

This study was designed and conducted in compliance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki (16). The study protocol was approved by the ethics committee of the Cannizzaro Hospital (Catania, Italy). Informed consent was obtained from centenarians or from their relatives (in cases resulting from illiteracy or difficulty in vision or hearing) before any study procedures were initiated.

Study design

This was a randomized, double-blind, placebo-controlled study. The study was conducted between 1999 and 2002, and the study participants, living in Sicily, were recruited through the Registry office. The 70 centenarians were randomly assigned by a computer-generated randomization schedule to receive a 6-mo supply of either levocarnitine or placebo.

The treatment was for 6 mo. The follow-up was for another 6 mo after treatment to evaluate survival. The measurements were made every month, both for efficacy tests and for tolerability.

Prerandomization phase

The subjects or the caregivers were required to document all caloric intake with the use of a diary, completed every 2 d. This prerandomization period was designed to nullify the effects of dietary changes on metabolic markers.

During the initial 2-wk phase, subjects (nurses or caregivers) were instructed by a dietitian to follow an ad libitum diet as classified by the National Cholesterol Education Program (Step 2). Subjects underwent weekly visits throughout the treatment period to assess adherence to the study protocol, to measure blood pressure and cognitive functions, and to record adverse events.

Randomization phase

Throughout the trial, L-carnitine was supplied in vials with 2 g carnitine (Sigma Tau, Rome, Italy) taken orally once a day. All drugs and placebos were identical in appearance, and neither investigators nor patients were informed of the selected agent until the end of the study phase.

Dosing instructions were provided with each patient pack. All trial medication was instructed to be taken as prescribed. Subjects were considered compliant if the number of returned vials was between 80% and 120% of the planned treatment regimen. For the duration of the trial any concomitant drugs were administered at the lowest possible therapeutic dosage and, as far as possible, were not changed.

L-Carnitine determination

Patients were studied in the morning between 0800 and 1000 after an overnight fast. The patients were first asked to empty their bladder. Then, venous blood samples were drawn into tubes containing EDTA or heparin, and serum or plasma was obtained by centrifugation (2000 $\times$ *g* for 5 min at 25 °C). A spot urine sample was obtained 10 min after the collection of the blood sample. Serum was measured immediately; plasma and urine were stored at −20 °C until analysis.

The L-carnitine concentration in plasma and urine was measured by a method described by Cederblad and Lindstedt (17) and modified by Brass and Hoppel (18). Plasma was treated with perchloric acid (final concentration of 3% vol:vol) and centrifuged for 2 min at 10 000 $\times$ *g* and at 25 °C. Long-chain acylcarnitines (LCACs) were measured in the pellet after alkaline hydrolysis, and free and short-chain acylcarnitines (SCACs) were measured in the supernatant fluid. The interassay CVs were 3.8%, 3.9%, and 4.1%, respectively; the intraassay CVs were 5.4%, 5.8%, and 6.4%, respectively. Addition of LCACs, together with the free and SCACs yields the total acyl-carnitine.

In urine no perchloric acid precipitation was performed (LCACs are normally not found in urine). Free carnitine and SCACs were measured in plasma. The within-assay CVs were 4.1% and 3.9%, respectively; the between-assay CVs were 5.2% and 5.8%, respectively.

The creatinine concentrations were measured by a kinetic colorimetric reaction in the same samples as used for the measurement of the L-carnitine concentrations. The within- and between-assay CVs were 3.9% and 5.4%, respectively. Seventy samples of centenarians were used to calculate the intraassay and interassay CVs.

Efficacy assessment

Throughout the randomization phase of the study, thriceweekly alimentary diary cards were used to collect efficacy data. The primary efficacy measures were changes in total fat mass, total muscle mass, triacylglycerols, total cholesterol, HDL cholesterol, and LDL cholesterol. Measurements were made at the beginning and at the end of the study period. Data were collected in the morning, after an overnight fast.

Anthropometric data were measured at baseline and at the end of the study period. The body mass index was calculated from body weight and body height. To measure total fat mass and total muscle mass, bioelectrical impedance analysis was used. Before measurement, subjects were instructed to refrain from physical activity for 12 h and liquids for 4 h and were asked to urinate 30 min before examination. For the 5 min leading up to the measurement period, subjects were told to adopt a supine position with their legs apart. After the skin was cleaned with 70% alcohol, 4 adhesive electrodes (3 M Red Dot T; 3 M Health Care, Borken, Germany) were placed on the surface of the right hand and right foot, according to the manufacturer's guidelines. We used a BioZ2 generator (Spengler, Paris, France). The interobserver and interday variability was 0.003 kg for fat-free mass (95% CI: −0.2, 0.2).

Physical and mental fatigue, the severity of fatigue, and the MMSE were assessed before and after treatment. Functional assessment was performed with the use of the Katz Index of Activities of Daily Living (ADLs; range: 0–6). ADL questions included walking, feeding, bathing, using the toilet, and dressing (19).

Tolerability assessment

Laboratory assessments were monitored at baseline and monthly until the end of the trial. These data included blood glucose, total cholesterol, HDL cholesterol, triacylglycerols, creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, alanineaminotransferase, alkaline phosphatase, creatinine, and blood urea nitrogen. Fasting plasma glucose was measured by the glucose-oxidase method. Serum total cholesterol and triacylglycerol concentrations were measured by the enzymatic method. HDL cholesterol was measured by the heparin-calcium method. Serum creatinine was measured by Jaffe reaction. Electrocardiogram and blood pressure were monitored with the use of standard techniques.

Physical activity was evaluated weekly with 6-min walking test (6MWT). The centenarians walked in a corridor of known length for 6 min. The 6MWT was performed in the morning after an overnight fast in a quiet room at a constant temperature of 22 ± 2 °C. The walking distance was the distance in meters walked by the centenarians in 6 min.

Statistical analysis

For all nonparametric data, discrete and continuous variables were compared with the use of either the Student's *t* test or Wilcoxon's Mann-Whitney test. Categorical variables were compared with the use of either the chi-square test or Fisher's exact test. STATISTICAL ANALYSIS SYSTEM software (version 6.11; SAS Institute, Cary, NC) was used for all analysis.

A repeated-measures 2-factor analysis was done. All *P* values were 2-sided, with the use of $\alpha = 0.05$ as the reference standard for determining the significance of the principal outcomes. The primary population for statistical analysis was an intention-to-treat population of all subjects randomly assigned.

RESULTS

Baseline characteristics

The baseline characteristics were evenly distributed across the 2 groups of enrolled patients. No significant differences between the 2 groups were observed before treatment (**Table 1**). In the comparison between the groups, we observed that the proportion in the local rest homes was 87.5% in the L-carnitine group compared with 79.4% in the placebo group, for those residing in the community was 12.5% compared with 20.6%, for those who were illiterate was 46.9% compared with 52.9%, for those with bad eyesight was 78.1% compared with 64.7%, for those with hearing loss 87.5% compared with 58.8%, for those with cognitive deterioration was 50% compared with 44.1%, in current or past smokers was 62.5% compared with 52.9%, respectively.

Plasma and clinical markers

Total cholesterol showed a significant decrease during the treatment with L-carnitine ($P < 0.01$; 95% CI, 0.17, 1.21) compared with placebo (**Table 2**).

TABLE 1
Baseline characteristics and basal plasma variables of L-carnitine and placebo cohorts at randomization[1]

	L-Carnitine ($n = 32$)	Placebo ($n = 34$)
Age (y)	101 ± 1.3[2]	101 ± 1.4
Sex (*n*)		
Men	10	11
Women	22	23
SBP (mm Hg)	155 ± 24.2	154 ± 25.1
DBP (mm Hg)	86.2 ± 10.1	84.7 ± 10.3
Heart rate (bpm)	88 ± 10	87 ± 12
BMI (kg/m^2)	22.2 ± 4.7	22.6 ± 4.1
BUN (mmol/L)	7.42 ± 3.14	7.01 ± 3.50
Plasma creatinine (μmol/L)	95.47 ± 49.50	84.86 ± 61.88
Blood glucose (mmol/L)	4.44 ± 1.45	4.68 ± 1.13
Total cholesterol (mmol/L)	4.87 ± 1.01	4.79 ± 1.04
HDL cholesterol (mmol/L)	1.27 ± 0.21	1.22 ± 0.21
Triacylglycerols (mmol/L)	1.51 ± 0.63	1.47 ± 0.64
CPK (IU/L)	45.4 ± 18.2	44 ± 20.1
LDH (IU/L)	341.2 ± 44.6	356 ± 40.2

[1] SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute; BUN, blood urea nitrogen; CPK, creatine phosphokinase; LDH, lactate dehydrogenase. *P* was not significant between the 2 treatment groups.
[2] $\bar{x}$ ± SD (all such values).

L-Carnitine in urine and plasma

In the levocarnitine group, significant differences were observed in the following markers after treatment compared with baseline: plasma concentrations of total L-carnitine (12.6 μmol/L), plasma LCAC (1.5 μmol/L), and SCAC (6.0 μmol/L). No significant differences of levocarnitine concentrations were observed in the urine.

In the placebo group the plasma concentrations of free L-carnitine and LCAC and the urinary excretion of free L-carnitine and SCAC did not show significant differences compared with baseline. At the end of the study period, compared with placebo, the levocarnitine-treated centenarians showed significant improvements in the following markers: plasma concentrations of total L-carnitine (12.60 compared with −1.70 μmol/L), LCAC (1.50 compared with −0.1 μmol/L), and SCAC (6.0 compared with −1.50 μmol/L). No significant differences of levocarnitine concentrations were observed in the urine (**Table 3**).

Physical performance and daily activity

In the levocarnitine group, significant differences were observed in the following markers after treatment compared with baseline. The total muscle mass increased by 3.8 kg. The total fat mass decreased by 1.8 kg, the ADLs increased by 0.5 points, the 6MWT increased by 4.4 m. In the placebo group the physical performance and daily activity did not show a significant difference from baseline.

At the end of the study period, compared with placebo, the levocarnitine-treated centenarians showed significant improvements in the following markers: total fat mass (−1.80 compared with 0.6 kg), total muscle mass (3.80 compared with 0.8 kg), plasma concentrations of total L-carnitine (12.60 compared with −1.70 μmol), LCAC (1.50 compared with −0.1 μmol), SCAC (6.0 compared with −1.50 μmol), ADLs (0.5 compared with 0.1), and 6MWT (4.4 compared with 0.4 m) (**Table 4**).

TABLE 2
Comparison of the plasma and clinical markers between treatment groups[1]

	L-Carnitine treatment ($n = 32$)		Placebo treatment ($n = 34$)	
	Before treatment	After treatment	Before treatment	After treatment
SBP (mm Hg)	158.2 ± 22.1	156.1 ± 21.8	151.4 ± 23.8	152.1 ± 24.7
DBP (mm Hg)	81.4 ± 11.1	80.2 ± 12.8	83.2 ± 10.7	82.8 ± 11.9
Heart rate (bpm)	85 ± 9	86 ± 8	84 ± 10	87 ± 8
BMI (kg/m^2)	22.3 ± 4.6	23.4 ± 4.2	22.8 ± 4.7	22.8 ± 43.1
Total cholesterol (mmol/L)	4.79 ± 1.06	4.10 ± 1.0[2]	4.84 ± 1.04	4.69 ± 1.04[3]
HDL cholesterol (mmol/L)	1.24 ± 0.10	1.28 ± 0.11	1.27 ± 0.21	1.27 ± 0.23
Triacylglycerols (mmol/L)	1.59 ± 0.44	1.50 ± 0.38	1.61 ± 0.45	1.60 ± 0.46
Plasma creatinine (mmol/L)	93.70 ± 44.2	90.17 ± 53.92	84.86 ± 60.11	79.56 ± 62.76
BUN (mmol/L)	7.65 ± 2.89	7.47 ± 2.97	7.19 ± 3.34	7.27 ± 3.25
Glucose (mmol/L)	4.65 ± 1.02	4.39 ± 1.04	4.67 ± 1.08	4.65 ± 1.01
CPK (IU/L)	45.1 ± 19.3	40.2 ± 18.2	43.8 ± 19.4	42.2 ± 18.7
LDH (IU/L)	358.1 ± 36.71	354.2 ± 38.2	354.1 ± 36.82	351.6 ± 39.6

[1] All values are $\bar{x}$ ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute; BUN, blood urea nitrogen; CPK, creatine phosphokinase; LDH, lactate dehydrogenase.
[2] Significantly different from before treatment, $P < 0.01$ (ANOVA).
[3] Significantly different from the L-carnitine group, $P < 0.05$ (ANOVA).

Fatigue

In the levocarnitine group significant differences were observed in the following markers after treatment compared with baseline: the score for the physical fatigue component of the Wessely and Powell Scale decreased by 4.10 points, whereas the mental score decreased by 2.70. The fatigue severity score decreased by 23.60.

In the placebo group no significant differences were observed compared with baseline. At the end of the study period, compared with placebo, the levocarnitine-treated centenarians showed significant differences in the following markers: physical fatigue (−4.10 compared with −1.10), mental fatigue (−2.70 compared with 0.30), and fatigue severity (−23.60 compared with 1.90) (Table 4).

Cognitive function

In the levocarnitine group significant differences were observed in the following marker after treatment compared with baseline: the MMSE score increased by 4.10. In the placebo group there were no significant differences compared with baseline. At the end of the study period, compared with placebo, the levocarnitine-treated centenarians showed significant improvements in the MMSE score (4.10 compared with 0.60) (Table 4).

Tolerability

Of the 70 patients randomly assigned, 3 withdrew their consent and 1 died; 66 received the treatment. In the group treated with L-carnitine, 5 subjects withdrew, 3 died (1 after 66 d of beginning treatment, 1 after 121 d, 1 after 156 d), 1 for side effects, and 1 withdrew consent (**Figure 1**).

In the group treated with placebo, 7 subjects withdrew, 5 died (1 after 36 d, 1 after 64 d, 1 after 85 d, 1 after 94 d, 1 after 110 d), 1 for side effects, and 1 withdrew consent. The 2 groups were homogeneous for baseline characteristics and clinical markers.

In the group treated with L-carnitine, 1 patient decided against continuing the treatment after diarrhea (diarrhea was a consequence of the treatment with levocarnitine). In the group treated

TABLE 3
Comparison of plasma and urinary concentrations of L-carnitine between treatment groups[1]

	L-Carnitine treatment ($n = 32$)		Placebo treatment ($n = 34$)			
	Before treatment	After treatment	Before treatment	After treatment	P for time[2]	P for group × time[2]
Free plasma carnitine (μmol/L)	41.8 ± 7.7[3]	49.2 ± 17.6	40.3 ± 8.4	43.3 ± 10.7	<0.05	NS
Plasma SCAC (μmol/L)	10.3 ± 5.1	16.3 ± 13.0[4]	10.1 ± 5.4	8.6 ± 2.9[5]	<0.01	<0.001
Plasma LCAC (μmol/L)	2.8 ± 0.7	4.3 ± 1.8[4]	3.0 ± 0.8	3.1 ± 0.9[5]	<0.001	<0.001
Total plasma carnitine (μmol/L)	55.2 ± 9.9	67.8 ± 29.9[4]	53.4 ± 12.5	55.1 ± 12.0[5]	<0.05	<0.05
Free urinary carnitine (μmol/L)	15.8 ± 9.6	16.7 ± 8.7	14.9 ± 10.6	13.2 ± 10.1	NS	NS
Urinary SCAC (μmol/L)	12.8 ± 7.1	13.2 ± 7.4	13.1 ± 9.4	12.0 ± 9.0	NS	NS

[1] SCAC, short-chain acylcarnitine; LCAC, long-chain acylcarnitine.
[2] Determined with ANOVA.
[3] $\bar{x}$ ± SD (all such values).
[4] Significantly different from before treatment.
[5] Significantly different from the L-carnitine group.

TABLE 4
Comparison of physical and mental markers and clinical characteristics between treatment groups[1]

	L-Carnitine treatment ($n = 32$)		Placebo treatment ($n = 34$)			
	Before treatment	After treatment	Before treatment	After treatment	P for time[2]	P for group × time[2]
Total fat mass (kg)	21.4 ± 3.8[3]	19.6 ± 3.9[4]	21.2 ± 3.6	21.8 ± 3.4[5]	NS	<0.01
Total fat-free mass (kg)	35.1 ± 3.2	38.9 ± 3.9[4]	35.4 ± 3.5	36.2 ± 3.9[5]	<0.001	<0.01
Physical fatigue score (0–16)	12.9 ± 2.6	8.8 ± 2.4[4]	12.7 ± 2.4	11.6 ± 2.5[5]	<0.001	<0.001
Mental fatigue score (0–16)	7.5 ± 2.1	4.8 ± 1.7[4]	7.4 ± 2.3	7.1 ± 2.0[5]	<0.001	<0.001
Fatigue Severity Scale (9–63)	54.2 ± 5.6	30.6 ± 9.4[4]	53.8 ± 5.2	51.9 ± 7.6[5]	<0.001	<0.001
MMSE (0–30 points)	16.4 ± 3.6	20.5 ± 2.9[4]	16.6 ± 2.9	17.2 ± 2.8[5]	<0.001	<0.001
Activity Index of Daily Living (score)	3.1 ± 0.4	3.6 ± 0.5[4]	2.9 ± 0.6	3.0 ± 0.4[5]	<0.001	<0.01
Walking distance (m)	10.2 ± 3.8	14.6 ± 3.9[4]	10.8 ± 3.4	11.2 ± 3.4[5]	<0.001	<0.001

[1] MMSE, Mini Mental State Examination.
[2] Determined with ANOVA.
[3] $\bar{x}$ ± SD (all such values).
[4] Significantly different from before treatment.
[5] Significantly different from the L-carnitine group.

with placebo a patient had bronchopneumopathy chronic obstructive, and for this reason treatment was discontinued. In the other subjects the repeated administration of levocarnitine was well tolerated with good compliance.

DISCUSSION

Centenarians are characterized by a general weakness, decreasing mental health, impaired mobility and balance, and poor endurance. In the centenarians the L-carnitine treatment improved total L-carnitine, SCACs, and LCACs, which dynamically interact with multiple coenzyme A–dependent biochemical pathways. L-Carnitine is required for mitochondrial long-chain fatty acid oxidation (6), a main source of energy during exercise (20). The increase in L-carnitine content might increase the rate of fatty acid oxidation, permitting a reduction of glucose utilization, preserving muscle glycogen content, and ensuring maximal rates of oxidative ATP production (21, 22, 23).

Under normal nutritional conditions and in healthy persons, L-carnitine availability is not a limiting step in β-oxidation; however, in centenarians its supplementation may provide beneficial effects. In fact, L-carnitine was shown to improve total muscle mass, reduce total fat mass with weight gain, and improve walking capacity.

L-Carnitine enhances exercise performance through SCAC production. The bioenergetic demands of exercise place stresses on the metabolic machinery of the muscle (24, 25). L-Carnitine treatment showed an improvement of performance levels (a measure of patient's daily activity) in these subjects, suggesting that abnormality in mitochondrial homeostasis was the basis of some

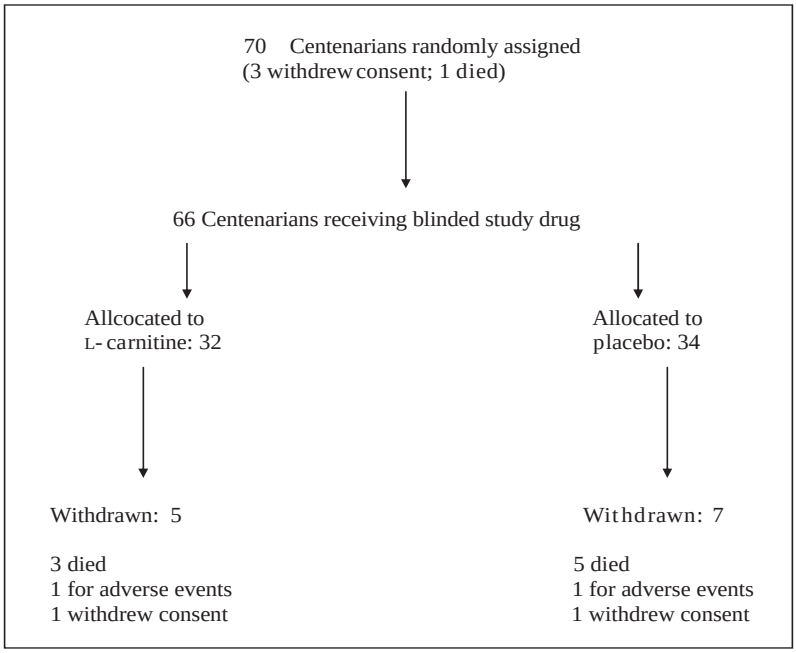

FIGURE 1. Trial profile of L-carnitine treatment.

symptoms, such as fatigue, depression, and sarcopenia, observed in the elderly and centenarians (26). When administered orally, L-carnitine enhances the performance efficiency of high-intensity muscular exercise.

The beneficial effects of L-carnitine treatment were observed not only in muscle metabolism but also in the myocardium (27, 28). In fact, supplementation of the myocardium with L-carnitine results in an increased tissue L-carnitine content that restores L-carnitine losses and lessens the severity of ischemic injury (29, 30). In brain tissue, the L-carnitine shuttle mediates translocation of the acetyl moiety from mitochondria into the cytosol and thus contributes to the synthesis of acetylcholine and of acetylcarnitine (31, 32). The neurobiologic effects of acetyl carnitine include modulation of brain energy and phospholipids metabolism, cellular macromolecules (such neurotrophic factors and neurohormones), synaptic morphology, and synaptic transmission of multiple neurotransmitters (33, 34).

Our study has several limitations. Our analyses were not adjusted for traditional risk factors, such as dyslipidemia and smoking, which we did not believe would be relevant in subjects aged $\geq$100 y and who represent a clinical end stage rather than a population at risk. Another limitation is the inclusion of subjects with mild cognitive deficits, bad eyesight, or hearing loss or who were illiterate. This would severely limit their ability to provide accurate answers on questionnaires about the primary outcomes. Furthermore, the centenarians were always assisted by relatives, nurses, or caregivers.

In our study, compared with baseline, we observed changes not only in both physical and mental fatigue but also in cognitive deterioration. In our previous study, we found that treatment with exogenous levocarnitine in elderly subjects was associated with an increase in total muscle mass and a significant reduction in muscle fatigue compared with placebo (8).

The beneficial effects of L-carnitine on heart function recovery from ischemia cannot be justified by these drugs, stimulating fatty acid oxidation only. L-Carnitine treatment improves not only the total L-carnitine serum concentrations but also acetylcarnitine serum concentrations. Moreover, the action of L-carnitine on the central nervous system can slow cognitive deterioration that occurs as a result of the normal physiologic aging of nervous cells. It also improves cardiac output and muscular function (26, 29).

In centenarians we detected stable urinary excretion of total, free, and acyl carnitine. This could be related to the difference between tissues about the uptake of and synthetic capacity for L-carnitine (35). The variation of storage and metabolism of L-carnitine between different tissues (hepatic, renal, cardiac, skeletal muscle, brain, and pancreatic) and possible unstable excretion may explain the lack of correlation between blood and urinary L-carnitine in our patients.

The administration of L-carnitine improves cardiac output and muscular function and reduces cognitive deterioration (31, 36). Our study indicates that oral administration of levocarnitine evokes a reduction of total fat mass, increases total muscular mass, and facilitates an increased capacity for physical and cognitive activity, by reducing fatigue and improving cognitive functions.

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