The Effect of L-Carnitine on Fat Oxidation, Protein Turnover, and Body Composition in Slightly Overweight Subjects

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We used a combined tracer technique with the stable isotopes ^{13}C and ^{15}N to gain further insight into the metabolic changes that accompany supplementation of L-carnitine. The aim of the present study was to investigate whether L-carnitine supplementation can influence fat oxidation, protein turnover, body composition, and weight development in slightly overweight subjects. Twelve volunteers received an individual regular diet either without or with L-carnitine supplementation of 3 g/d for 10 days. Protein turnover and fat oxidation were investigated after administration of [^{15}N]glycine and an [U-^{13}C]algae lipid mixture. The ^{15}N- and ^{13}C-enrichment in urine and breath were measured by isotope ratio mass spectrometry. Body fat mass (BFM), total body water (TBW), and lean body mass (LBM) were calculated by using bioelectric impedance analysis. L-carnitine supplementation led to a significant increase in ^{13}C-fat oxidation (15.8% *v* 19.3%; *P* = .021) whereas protein synthesis and breakdown rates (3.7 and 3.4 g/kg/d, respectively) remained unchanged, indicating that the increased dietary fat oxidation in slightly overweight subjects was not accompanied by protein catabolism.

L-CARNITINE IS A naturally occurring substance required for energy metabolism in mammals. It is produced by the body and is also available in the diet mainly in products of animal origin. L-Carnitine is essential for the transport of long chain fatty acids across the mitochondrial membrane for subsequent fat degradation and energy production.[1] Another important function of L-carnitine is the ability to shuttle short chain fatty acids from inside the mitochondria to the cytosol. Therefore, L-carnitine is responsible for maintaining energy metabolism of the whole body.[2]

The potential positive effects of L-carnitine on fat turnover are presently under intensive scientific investigation.[3] Several studies have been published in recent years suggesting that L-carnitine supplementation can influence lipid metabolism and can also effect body composition.[4] Only few results are available so far on the effect of L-carnitine supplementation on weight reduction and body composition. Lurz and Fischer[5] observed body weight (BW) reduction after L-carnitine supplementation in obese subjects when following a calorie-restricted diet in the course of a weight management program.[5]

In a recently published report, Müller et al[6] observed for the first time an increase in fatty acid oxidation after L-carnitine supplementation of 3 g/d for 10 days in healthy adults without L-carnitine deficiency. After oral pulse labeling with [1-^{13}C]palmitic acid, they used the resulting cumulative percentage $^{13}CO_2$-exhalation to evaluate the total long chain fatty acid oxidation.[6]

However, little is known about the changes of fat oxidation and protein turnover after L-carnitine supplementation in slightly overweight subjects. The aim of the present study was, therefore, to investigate whether L-carnitine supplementation can influence fat oxidation, protein turnover, body composition, and weight development in slightly overweight subjects.

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MATERIALS AND METHODS

Subjects

Twelve slightly overweight subjects (7 females, 5 males; age, 18 to 30 years; body mass index, 24 to 27 kg/m^2), weight-stable for at least 1 month, volunteered for this study. None of the subjects was receiving any medication or had a history of gastrointestinal diseases. They were in good health throughout the study. Furthermore, none of the subjects complained about any gastrointestinal problems.

The testing protocol was approved by the Committee on Ethics of the Faculty of Medicine of the University of Rostock.

Experimental Protocol

All volunteers received an individual regular diet at 8 AM, 12 AM, and 6 PM for 10 days (carbohydrate/fat/protein ratio: 57%/30%/13%) without L-carnitine supplementation. BW of the subjects was determined on a pair of scales on the first and tenth day at 6:30 AM after an overnight fast. After 8 days of standardized diet, baseline breath and urine samples were collected on the ninth day 10 minutes before the ingestion of both stable isotope-labeled substances to determine the baseline abundance of ^{15}N and ^{13}C.

During breakfast, [^{15}N]glycine and an [U-^{13}C]algae lipid mixture (99 atom-% each, Campro Scientific, Berlin, Germany) were administered simultaneously as a single oral pulse labeling on the ninth day at 8 AM in a dosage of 0.5 mg/kg ^{15}N and ^{13}C each.

Urine was collected at 2-, 4-, and 6-hour intervals over a period of 36 hours after administration of the stable isotope-labeled substances. The urine volumes were recorded, and 10 mL of each sample was stored at −20°C until analysis.[7-9] Two expired breath samples by direct exhalation into Exetainers (PDZ Europa, Sandbach, UK) were collected at 30-minute intervals over a period of 14 hours.[10-12]

In a subsequent study phase, the same 12 subjects who had been on a 10-day individual regular diet regimen without L-carnitine supplementation then received on the 11th day together with breakfast, lunch, and dinner, 1.5 g L-carnitine-L-tartrate (Lonza, Basle, Switzerland) equivalent to 3 × 1 g/d L-carnitine, with the same individual diet. The subjects were weighed at the end of the L-carnitine supplementation period at 6:30 AM after an overnight fast.

Both trial periods were performed for 10 days to adjust the volunteers approximately to steady state conditions. Food intake was monitored to ensure equal caloric fuel ratio of protein to fat to carbohydrate in the absence of L-carnitine and during L-carnitine supplementation. The procedure of baseline breath and urine collection prior to tracer

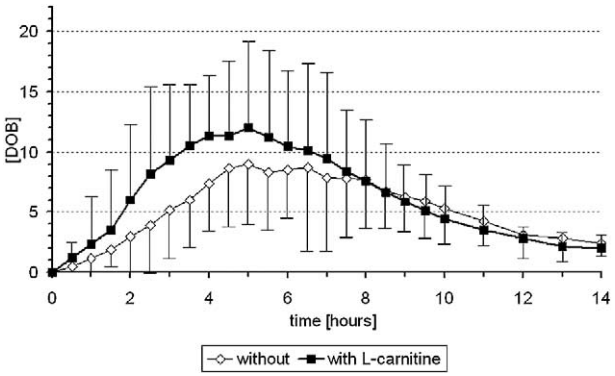

Fig 1. Mean $^{13}CO_2$-enrichment either without or with L-carnitine supplementation.

administration on the 19th day and the subsequent breath and urine collection were identical to the study that was performed without L-carnitine supplementation.

Analytical Techniques

Bioelectric impedance analysis. Body fat mass (BFM), total body water (TBW), and lean body mass (LBM) were estimated by using bioelectric impedance analysis (BIA 2000-M, Data Input GmbH, Frankfurt/Main, Germany) with high accuracy.[13,14] Measurements were performed from the right hand to the right foot at 6:30 AM after an overnight fast before and after 10 days of the regular diet and after the L-carnitine supplementation period.

Isotope Ratio Mass Spectrometry

The ^{15}N- and ^{13}C-enrichment in urine and breath were measured by isotope ratio mass spectrometry (Tracer mass 20-20; PDZ Europa, Sandbach, UK) as detailed previously.[10,11,15,29] The precision for ^{13}C and ^{15}N is 0.02% and 0.05%, respectively. An analytical grade urea standard (Serva Feinbiochemica GmbH, Heidelberg, Germany) calibrates both elemental composition and isotopic abundance for solid samples, whereas a 5 vol-% CO_2-standard gas is calibrated to allow delta values to be quoted against the Pee Dee Belemnite standard (PDB).[15]

The data were expressed either as enrichment $\delta\ ^{13}C$ and $\delta\ ^{15}N$ over baseline (DOB), as percentage dose recovery in breath, or as cumulative urinary ^{13}C- and ^{15}N-excretion.

Whole-Body Protein Turnover

In our study [^{15}N]glycine was used as the stable isotope-labeled substance for measuring whole-body protein turnover (Q). The whole-body protein turnover was calculated by using a 3-compartment model as previously described.[7-9]

The dietary protein input into the metabolic pool of the body is denoted by (I). Some of this protein input is used for protein synthesis (S), and some is excreted in the urine (E). The nitrogen flow out of the protein pool consists of nitrogen resulting from protein breakdown (B). Thus, the following equation results:

$$Q = S + E = B + I.^{7-9}$$

^{13}C-Fat Oxidation

The [U-^{13}C]algae lipid mixture used for measuring ^{13}C-fat oxidation contains 1 saturated and 3 unsaturated uniformly ^{13}C-labeled fatty acids (50% palmitic acid, 27% oleic acid, 9% palmitoleic acid, and 13% linoleic acid) as the most predominating long-chain fatty acids of cow's milk and of human subcutaneous fat tissue.

The ^{13}C-fat oxidation was calculated according to the equations of Brösicke[17] and Radke et al.[16] The $^{13}CO_2$-excess exhalation rate ($^{13}CO_2ER$) is the product of an assumed CO_2-production rate (CO_2PR) of 300 mmol/m^2/h,[16-19] the calculated cumulative ^{13}C-data ($\Delta\delta^{13}C_{cum}$), the isotope ratio of $^{13}CO_2$ standard gas (0.01123), and the body surface area (BSA) in square meter divided by the ^{13}C-excess dose (D) in millimole times 10:

$$^{13}CO_2ER = CO_2PR \cdot \Delta\delta^{13}C_{cum} \cdot (0.01123) \cdot BSA/10D\ .$$

$$\Delta\delta^{13}C_{cum} = \sum_{i=1}^{n} \tfrac{1}{2}(\Delta\delta^{13}C_{ti-1} + \Delta\delta^{13}C_{ti}) \cdot (t_i - t_{i-1})\ .$$

$\Delta\delta^{13}C_{ti}$ is $\delta^{13}C_{ti} - \delta^{13}C_{t0}$ the ^{13}C-enrichment at time t_i and the ^{13}C zero excess exhalation at time t_0 which is 0.

Statistical Analysis

The paired *t* test was used for statistical analysis.

RESULTS

The mean maximum $^{13}CO_2$-enrichments either without or with L-carnitine supplementation of 9 and 12 DOB, respectively, were reached after 5.0 hours, and elevated levels were still detectable after 14 hours (Fig 1). The maximum $^{13}CO_2$-peaks either without or with L-carntine supplementation were reached simultaneously after 5 hours.

The L-carnitine supplementation led to a significantly increased ^{13}C-fat oxidation (15.8% *v* 19.3%; $P = .021$) measured by the percentage cumulative $^{13}CO_2$-exhalation method (Table 1, Fig 2). There was no significant gender difference in $^{13}CO_2$-

Table 1. Gender, Body Mass Index, and Percentage Cumulative $^{13}CO_2$-Exhalation in 12 Subjects Either Without or With L-Carnitine Supplementation

Initials	Gender	BMI (kg/m^2)	Without (%)	With L-Carnitine (%)
SH	F	26.9	14.7	17.3
AM	F	26.3	9.5	6.3
MK	F	26.2	13.2	16.0
AP	F	25.0	14.2	26.6
RB	F	24.4	22.1	28.9
AJ	F	24.3	18.7	20.0
NO	F	23.9	16.8	22.1
Mean	F	25.3	15.6†	19.6‡
SD		1.2	4.1	7.5
CL	M	25.7	3.1	12.4
GH	M	25.5	17.6	17.0
OH	M	25.2	16.7	19.8
NL	M	24.9	22.1	21.0
FS	M	24.2	20.8	24.0
Mean	M	25.1	16.1†	18.8‡
SD		0.6	6.8	3.9
General mean (both sexes)		25.3	15.8*	19.3*
SD		1.0	5.5	6.2

*$P = .021$.
†$P = .686$.
‡$P = .684$.

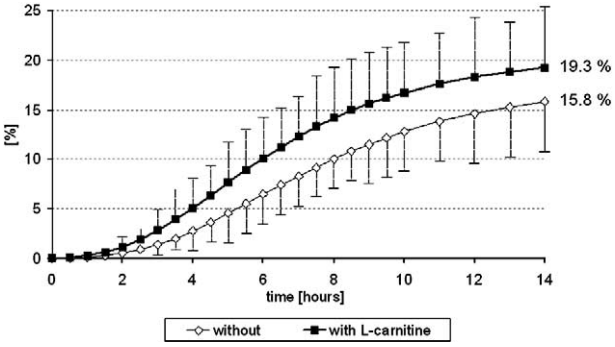

Fig 2. Percentage cumulative $^{13}CO_2$-exhalation either without or with L-carnitine supplementation.

exhalation (without L-carnitine: 15.6% for females *v* 16.1% for males, $P = .686$; with L-carnitine: 19.6% *v* 18.8%, $P = .684$, respectively, Table 1).

BFM (21.3 ± 4.8 *v* 21.5 ± 5.1 kg), LBM (58.1 ± 10.8 *v* 58.3 ± 10.6 kg), TBW (42.5 ± 7.9 *v* 42.7 ± 7.8 L), and BW (79.4 ± 10.5 *v* 79.7 ± 11.5 kg) remained unchanged after L-carnitine supplementation (Table 2).

The calculated S rates (3.7 *v* 3.7 g/kg/d), B rates (3.4 *v* 3.4 g/kg/d), and N (0.3 *v* 0.2 g/kg/d) calculated using the 3-compartment model were identical (Table 3). All volunteers tolerated the L-carnitine supplementation well. Satiety was reported as sufficient.

DISCUSSION

Scientific investigations conclude that L-carnitine may decrease fat deposition in favor of protein deposition.[20] Moreover, L-carnitine supplementation favorably affects markers of recovery from exercise stress.[21,22] Sources of L-carnitine for humans include endogenous synthesis, consumption of foods of animal origin, or consumption of dietary supplements.[1-6]

The Research Laboratory of the Children's Hospital of the University of Rostock has many years experience in using stable isotopes for measuring protein turnover and fat oxidation in both children and adults.[7-10]

In the present study, we used the combination of measuring fat oxidation, protein turnover rates, and body composition to gain further insight into the metabolic changes that accompany the ingestion of dietary supplements, such as L-carnitine. All subjects underwent an initial isotope study in the absence of L-carnitine followed by a subsequent study with L-carnitine supplementation. This order was chosen to keep the design as close as possible to the study of Müller et al.[6] One of the objectives of our study was to verify the results obtained by Müller et al and to evaluate whether this method could be used for further investigations of the effects of L-carnitine on fatty acid oxidation in various population groups. However, our combination of measuring fatty acid oxidation, protein turnover, and body composition simultaneously after L-carnitine supplementation is a novelty.

Table 2. BFM, LBM, TBW, and BW in 12 Subjects Either Without or With L-Carnitine Supplementation

	Without				With L-Carnitine			
	BFM (kg)	LBM (kg)	TBW (L)	BW (kg)	BFM (kg)	LBM (kg)	TBW (L)	BW (%)
Mean	21.3	58.1	42.5	79.4	21.5	58.3	42.7	79.7
SD	4.8	10.8	7.9	10.5	5.1	10.6	7.8	11.5

Abbreviations: BFM, body fat mass; LBM, lean body mass; TBW, total body water; BW, body weight.

Table 3. Mean Protein Synthesis Rate (S), Protein Breakdown Rate (B), and Net Protein Gain (N) in 12 Subjects Either Without or With L-Carnitine Supplementation

	Without			With L-Carnitine		
	S (g/kg/d)	B (g/kg/d)	N (g/kg/d)	S (g/kg/d)	B (g/kg/d)	N (g/kg/d)
Mean	3.7	3.4	0.3	3.7	3.4	0.2
SD	1.5	1.4	0.3	1.1	1.1	0.4

The use of stable isotopes to obtain information regarding the protein and fatty acid metabolism is based on the assumption that the stable isotope-labeled substance used should be representative for the system as a whole.[7-10] [^{15}N]glycine was found to be an appropriate and reliable tracer substance when used in adults.[23-28] Therefore, in our study [^{15}N]glycine was used as representative tracer substance for measuring S and B rates during consumption of an individual regular diet either without or with L-carntine supplementation.[29] Additionally, a uniformly [U-^{13}C]algae lipid mixture was used for this reason to ensure a representative measurement of total ^{13}C-fat oxidation.[29] It differs from the single palmitic acid (^{13}C-labeled in 1-position only) used by Müller et al.[6] The particular advantage of applying a mixture of 4 uniformly ^{13}C-labeled fatty acids is the fact that the ^{13}C-dose is spread among all carbon atoms, which gives a more representative picture of fat metabolism in contrast to the use of a single fatty acid.[10]

When considering the results of the present study by using an [U-^{13}C]algae lipid mixture, the results for the percentage cumulative $^{13}CO_2$-exhalation either without or with L-carnitine supplementation (15.8% *v* 19.3%) were significantly different from those for [1-^{13}C]palmitic acid (5.1% *v* 7.0%) reported by Müller et al.[6] This typical response of a relatively low $^{13}CO_2$ exhalation reflects the specific oxidation and the respective disappearance of [1-^{13}C]palmitic acid in the fatty acid pool of the body. Moreover, several studies demonstrated that long-chain ^{13}C-labeled saturated fatty acids are not absorbed as well as ^{13}C-labeled unsaturated fatty acids.[10,30] Our [U-^{13}C]algae lipid mixture consists of 49% unsaturated free fatty acids (27% oleic acid, 9% palmitoleic acid, and 13% linoleic acid). A higher absorbtion of these unsaturated fatty acids would explain the higher percentage $^{13}CO_2$-recovery in comparison to saturated [1-^{13}C]palmitic acid (15.8% *v* 5.1%). Nevertheless, the different metabolic fate of the ^{13}C-labeled algae fatty acids may also have affected the differences in recovery of label in breath.

The observed $^{13}CO_2$ recovery rates in expired air suggest that the main part of the ^{13}C-labeled fatty acids is deposited in adipocytes of fat tissue, retained in the body bicarbonate pool or in other metabolic pathways and is excreted in feces.[10]

The calculated [1-^{13}C]palmitic acid oxidation rates were found to be similar to the values described by other investigators.[30,31]

Using single ^{13}C-fatty acids for evaluating the rate of fat oxidation might cause fatty acid imbalances due to the relatively high dosage applied. Müller et al administered 1 g [1-^{13}C]palmitic acid per subject, whereas in our study, merely 0.7 mg [U-^{13}C]algae lipid mixture per kilogram BW was used. The maximum $^{13}CO_2$-peaks either without or with L-carntine supplementation were reached simultaneously after 5 hours showing that an L-carnitine dosage of 3 g/d does not accelerate the oro-caecal transit time (Fig 1).

However, although using different ^{13}C tracer substances, both Müller's study and ours revealed a significantly increased fat oxidation after L-carnitine supplementation. The measured $^{13}CO_2$-exhalation over 14 hours reflects mainly the dietary fat oxidation.[10]

Müller et al observed that L-carnitine supplementation increased serum L-carnitine and acyl-L-carnitine levels, as well as increased urinary L-carnitine excretion.[6] Whether this promotes an increase in fatty acid oxidation in healthy subjects remains open. As a results of these data and in order to maintain the noninvasive character of our study, we did not take blood samples.

Our observation of an increased fat oxidation during L-carnitine supplementation does not correspond to the findings of unchanged BFM, TBW, LBM, and BW within a 10 day L-carnitine supplementation period. However, 10 days is a relatively short period of supplementation, prolonged supplementation may beneficially influence BW, as found by Lurz and Fischer[5] in obese subjects. Further studies need to evaluate this hypothesis.

When considering the S and B rates of the subjects on both supplemental periods, no differences in the protein turnover rates were observed, clearly indicating that the increased fat oxidation observed after L-carnitine supplementation is not accompanied by protein catabolism.[3-6] Our calculated values were found to be similar to the data described earlier by other investigators for regular diets.[27,28]

In contrast to the unchanged protein turnover rates, the L-carnitine supplementation led to an increased ^{13}C-fat-oxidation (15.8% *v* 19.3%; $P = .021$) corresponding to an improved dietary fat utilization. In a recently published report, similar fat oxidation rates were obtained when using a [U-^{13}C]algae lipid mixture on a regular diet (15%).[29] L-carnitine supplementation increases the rate of dietary fat oxidation in this population.

To evaluate the metabolic changes of an energy and protein-reduced diet with L-carnitine supplementation, further studies in obese subjects are in preparation.

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