Long-term administration of L-carnitine to humans: effect on skeletal muscle carnitine content and physical performance

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Abstract

Background: Long-term administration of high oral doses of L-carnitine on the skeletal muscle composition and the physical performance has not been studied in humans. Methods: Eight healthy male adults were treated with 2 × 2 g of L-carnitine per day for 3 months. Muscle biopsies and exercise tests were performed before, immediately after, and 2 months after the treatment. Exercise tests were performed using a bicycle ergometer for 10 min at 20%, 40%, and 60% of the individual maximal workload (P_max), respectively, until exhaustion. Results: There were no significant differences between VO2_max, RER_max, and P_max between the three time points investigated. At submaximal intensities, the only difference to the pretreatment values was a 5% increase in VO2 at 20% and 40% of P_max 2 months after the cessation of the treatment. The total carnitine content in the skeletal muscle was 4.10 ± 0.82 μmol/g before, 4.79 ± 1.19 μmol/g immediately after, and 4.19 ± 0.61 μmol/g wet weight 2 months after the treatment (no significant difference). Activities of the two mitochondrial enzymes citrate synthase and cytochrome oxidase, as well as the skeletal muscle fiber composition also remained unaffected by the administration of L-carnitine. Conclusions: Long-term oral treatment of healthy adults with L-carnitine is not associated with a significant increase in the muscle carnitine content, mitochondrial proliferation, or physical performance. Beneficial effects of the long-term treatment with L-carnitine on the physical performance of healthy adults cannot be explained by an increase in the carnitine muscle stores. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: L-Carnitine; Long-term treatment; Skeletal muscle; Carnitine

1. Introduction

L-Carnitine (R(−)-3-hydroxy-4-trimethylaminobutyrate) is found ubiquitously in mammalian tissues and represents an important factor in the cellular energy metabolism [1]. Carnitine is essential for the transport of the long-chain fatty acids across the inner mitochondrial membrane into the mitochondrial matrix, the site of β-oxidation [2]. In agreement with this important function of carnitine, carnitine deficiency in humans is associated with myopathy [3] and impaired fatty acid oxidation [4].

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Another important function of carnitine is the buffering of the activated short-chain carboxylic acids as acylcarnitines [5,6]. Short-chain acylcarnitines are generated by the action of carnitine acetyl-CoA transferase, an enzyme located in the mitochondria, peroxisomes, and cytosol [7]. This reaction liberates free CoA (CoASH) which is an important substrate for different steps in mitochondrial energy metabolism such as pyruvate dehydrogenase and fatty acid oxidation. Acylcarnitines can be exported from the mitochondria and from cells into the plasma and are finally excreted by the kidney. Acetyl-CoA is an important intermediate in glucose and fatty acid metabolism and normally undergoes a complete oxidation in the Krebs cycle in the skeletal muscle. During exercise above the lactate threshold, generation of acetyl-CoA exceeds the capacity of the Krebs cycle, leading to an increase in the skeletal muscle lactate, acetyl-CoA and acetylcarnitine content [8–12]. These metabolic changes may limit the working capacity of the skeletal muscle since the accumulated acetyl-CoA inhibits the activity of the pyruvate dehydrogenase [13]. Under these conditions, the acetyl-CoA/CoASH ratio shows a linear correlation with the acetylcarnitine/carnitine ratio [11,12]. Therefore, if the skeletal muscle free carnitine pool could be increased, the CoASH pool should also rise, potentially resulting in an increased working capacity.

In agreement with this concept, Brass et al. [14] described increased force generation and decreased fatigability by isolated rat soleus skeletal muscle incubated in a buffer containing 10 mmol/l L-carnitine. Furthermore, Broderick et al. [15] demonstrated increased oxidative metabolism of glucose and improved function of isolated rat hearts perfused with a solution containing 10 mmol/l L-carnitine.

With few exceptions [16–19], short-term administration of L-carnitine for up to 2 weeks failed to show an increase in the working capacity or endurance performance in humans [20–25]. As shown by Brass et al. [23], intravenous administration of a single dose of L-carnitine is not associated with an increase in the carnitine skeletal muscle content in humans. The results of studies with long-term administration of L-carnitine are conflicting. Studies in patients with chronic hemodialysis suggest that the administration of L-carnitine over months can increase the skeletal muscle carnitine content [26]. In support of this concept, administration of L-carnitine for several months has been shown to improve the physical performance and to have a trophic effect on the skeletal muscle in patients on long-term hemodialysis [27,28] or suffering from peripheral arterial disease [29]. Similar findings were obtained in endurance athletes, in whom treatment with 2–4 g of L-carnitine for 4 weeks was associated with increased activities of mitochondrial enzymes, compatible with mitochondrial proliferation [30,31]. On the other hand, oral administration of 2 g of L-carnitine per day for 4 months to endurance athletes or sprinters did not affect the skeletal muscle carnitine content at rest but prevented the muscle exercise-associated losses of carnitine by an unexplained mechanism [32].

We therefore decided to investigate the effect of a long-term administration of high doses of L-carnitine on the skeletal muscle carnitine pool, skeletal muscle composition, and physical performance of male healthy human subjects. The study was designed to answer the following specific questions. (i) Does long-term administration of L-carnitine increase the skeletal muscle carnitine content? (ii) Is this increase associated with improved physical performance? (iii) Are there any signs of skeletal muscle mitochondrial proliferation?

2. Materials and methods

2.1. Subjects

Eight moderately trained healthy male subjects with an age of 23–25 years volunteered for this study. All subjects performed exercise tests on a regular basis but none was involved in a competitive athleticism. The study was approved by the Ethical Committee of the Medical Faculty at the University of Berne. All subjects were fully informed about the study’s purpose and its possible risks prior to giving their written consent.

2.2. Preliminary testing

Each subject underwent an initial grading test to determine his individual maximal workload ($P_{\text{max}}$). Exercise testing was performed until exhaustion on an electrically braked bicycle ergometer (Ergoline®, LMT Leuenberger Medizin Technik AG, Wallisellen, Switzerland). After a warmup period with loadless pedalling for 2 min, the grading procedure was started at 70 W
Heart rate, ventilation (VE), oxygen consumption ($V_{O2}$), carbon dioxide production ($V_{CO2}$), and the respiratory exchange ratio (RER, calculated as $V_{CO2}/V_{O2}$) were monitored continuously during the exercise by standard techniques of open circuit spirometry (Oxycon®, Pilger Medizin Elektronik AG, St. Gallen, Switzerland). $P_{max}$ was determined as the maximal workload at exhaustion. The oxygen and carbon dioxide analyzers were calibrated before and after every exercise test with standard gases of known concentration. Blood lactate concentrations were determined in the capillary blood obtained from a finger tip every 30 s before increasing the workload (YSI Model 23L®, IG Instrumentengesellschaft AG, Zürich, Switzerland). The lactate threshold was determined as the workload at a blood lactate concentration of 2 mmol/l [33]. After the calculation of 20%, 40%, and 60% of each subject’s $P_{max}$, an individual exercise protocol was designed for each subject for subsequent testing, as described in the next section.

### 2.3. Experimental protocol

One month after the initial grading, a needle biopsy was performed at rest in the right vastus lateralis muscle using a Bergström needle. Urine samples were collected and blood was taken from an antecubital vein. Subsequently, the subjects performed a submaximal exercise test for 10 min at 20%, 40%, and 60% of their individual $P_{max}$. After completion, the test was continued with increments of 30 W/2 min until exhaustion. Heart rate, VE, $V_{O2}$, $V_{CO2}$, and RER were determined continuously during the exercise test. Blood lactate concentrations were determined 1 min or 30 s before increasing the workload in the submaximal or the subsequent maximal exercise performance test, respectively.

From the day after the exercise test, the participants had to ingest $2 \times 2$ g of l-carnitine per day for the next 3 months (tablets containing 1 g of l-carnitine supplied by Sigma Tau, Zofingen, Switzerland). To ensure compliance, participants were asked to record their intake of tablets, tablets were counted, and spot urine and blood samples were obtained at different occasions. At the end of the treatment, a second needle biopsy was performed and urine and blood samples were obtained, as described above. Physical performance of the subjects was tested using the same protocol, as described above.

After a washing out period of 2 months, a third needle biopsy was performed in a subgroup ($n=6$) of the participants. Also at this time point, urine and blood samples were obtained from each participant and exercise tests were performed, as described above.

### 2.4. Sample preparation

For the determination of the blood lactate concentrations, capillary blood samples were withdrawn from a finger tip and analyzed immediately. For the determination of the free carnitine and acylcarnitine concentrations, blood samples were kept in ice until centrifugation (10 min at 3500 rpm) and the plasma was stored at $-20 \, ^{\circ}C$ until analysis. Urine samples were stored at $-20 \, ^{\circ}C$ until analysis for carnitine. Muscle biopsies were frozen immediately in liquid nitrogen and stored at $-70 \, ^{\circ}C$ until analysis.

### 2.5. Determination of carnitine

In plasma and urine, free carnitine, the short and medium chain acylcarnitine profile and total carnitine were determined by high-performance liquid chromatography, as described by Minkler and Hoppel [34]. Briefly, aliquots of plasma or diluted urine (1:10 with water) were treated with 1 ml acetonitril/methanol (3:1) and carnitine and acylcarnitines were extracted using columns containing 300 mg of silica gel. After evaporation to dryness, the samples were derivatized with 4'-bromophenacyl trifluoromethanesulfonate and quantified by the high-performance liquid chromatography with spectrophotometric detection. Aliquots of each sample were also subjected to alkaline hydrolysis before starting the extracting procedure in order to determine the total carnitine concentration. After hydrolysis, samples were treated exactly like the non-hydrolyzed aliquots. All samples were determined at least twice with an individual workup for every determination.

The carnitine content in the skeletal muscle was determined by three different methods. Free carnitine and short- and long-chain acylcarnitines were determined by the radioenzymatic assay, as originally described by Cederblad and Lindstedt [35] with the modifications of Brass and Hoppel [36]. The workup of the skeletal muscle samples was performed, as described by Hoppel [37]. Skeletal muscle samples were homogenized in 3% perchloric acid (w/v) and the
homogenate centrifuged at 15,000 × g for 2 min. In the supernatant, free carnitine was determined after the neutralization and the total acid soluble carnitines after the alkaline hydrolysis and neutralization. The short-chain acylcarnitine concentration was calculated by the subtraction of the free from the total acid soluble carnitine concentration. In the pellet, the long-chain acylcarnitine content was determined after alkaline hydrolysis and neutralization. The total carnitine concentration was calculated as the sum of the long-chain acylcarnitine and the total acid soluble carnitine concentrations.

For the quantification of free carnitine by in vitro NMR spectroscopy, separate muscle samples were worked up, as described above for the radioenzymatic assay. The carnitine content was determined in the acidic and neutralized supernatants using the peak integrations of the trimethylammonium peak of carnitine [38] and the methyl proton peaks of creatine and phosphocreatine which were determined in the same spectrum. Total creatine, i.e., the sum of creatine plus phosphocreatine, served as the internal reference for the normalization of carnitine.
Eight healthy male volunteers were treated with L-carnitine (2 g/C2/C2/C2/day) for 3 months. Bicycle ergometry was performed before, immediately after, and 2 months after stopping L-carnitine. Bicycle ergometry was performed for 10 min at 20%, 40%, and 60% of the previously determined PMAX until exhaustion, as described in Materials and methods. Data are given as the mean ± S.D. No significant differences between the different time points could be detected.

### 2.7. Statistical analysis

Values are reported as the mean ± S.D. Subjects served as their own controls by comparing the values at the end of the treatment with L-carnitine or after the 2-month washing out period with those before the treatment. Means were compared first with ANOVA for the repeated measurements followed by Student’s t tests for paired data.

### Table 3

<table>
<thead>
<tr>
<th>Skeletal muscle carnitine content</th>
<th>Before treatment (n = 8)</th>
<th>End of treatment (n = 7)</th>
<th>2 months after end of treatment (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radioenzymatic determination</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Free carnitine</td>
<td>3.29 ± 0.71</td>
<td>3.49 ± 1.22</td>
<td>3.35 ± 0.86</td>
</tr>
<tr>
<td>Short-chain acylcarnitines</td>
<td>0.64 ± 0.43</td>
<td>1.10 ± 0.75</td>
<td>0.73 ± 0.42</td>
</tr>
<tr>
<td>Total acid soluble carnitine</td>
<td>3.92 ± 0.78</td>
<td>4.59 ± 1.12</td>
<td>4.07 ± 0.59</td>
</tr>
<tr>
<td>Long-chain acylcarnitines</td>
<td>0.18 ± 0.09</td>
<td>0.20 ± 0.12</td>
<td>0.12 ± 0.10</td>
</tr>
<tr>
<td>Total carnitine</td>
<td>4.10 ± 0.82</td>
<td>4.79 ± 1.19</td>
<td>4.19 ± 0.61</td>
</tr>
<tr>
<td><strong>MR spectroscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carnitine/total creatinine</td>
<td>0.595 ± 0.104</td>
<td>0.596 ± 0.173</td>
<td>0.579 ± 0.099</td>
</tr>
</tbody>
</table>

Healthy subjects (n = 8) were treated with oral L-carnitine (2 × 2 g/day for 3 months). The skeletal muscle carnitine pool was determined radioenzymatically or by in vitro MR spectroscopy, as described in Materials and methods. Total acid soluble carnitine is the sum of the free carnitine and the short-chain acylcarnitine. Total carnitine is the sum of the total acid soluble carnitine and the long-chain acylcarnitine. Units are μmol/g muscle wet weight. Data are presented as the mean ± S.D. No significant differences between the different time points could be detected.
3. Results

3.1. Carnitine in urine and plasma

The carnitine concentration in the plasma and carnitine excretion in urine increased during the supplementation of carnitine, suggesting that the subjects were compliant. As shown in Fig. 1a, the carnitine plasma concentration doubled during the treatment due to increases in both the free carnitine and acylcarnitines. Two months after stopping the treatment, the total carnitine plasma concentration was not significantly different from the pretreatment, whereas the free carnitine concentration was still increased.

Renal excretion of carnitine was estimated by normalizing the carnitine concentration in the urine to the respective creatinine concentration (Fig. 1b). Similar to the plasma concentrations, there was an increase in the excretion of the total and free carnitine during the treatment with L-carnitine. Two months after stopping the administration of L-carnitine, renal carnitine excretion had reached pretreatment values again.

3.2. Physical performance

Initial grading had to be performed in order to design the final exercise protocols. The results of the initial tests are given in Table 1. These values are in agreement with the values obtained in a similar group of healthy humans reported previously [12].

The three subsequent test sessions consisted of exercise tests at 20%, 40%, and 60% of the individual $P_{max}$ followed by the exercise tests to exhaustion in order to determine $P_{max}$ and $V_{O2,max}$. As shown in Table 2, when compared to the pretreatment values after 3 months of L-carnitine supplementation, there were no significant changes in $V_{O2}$, RER, blood lactate concentration, or heart rate in the submaximal...
range, as well as at the maximal workload. Also, $P_{\text{max}}$ was not significantly different from the pretreatment values at this time point.

Two months after the treatment period, there was a 5% increase in $V_{O_2}$ at submaximal workloads (40% and 60% of $P_{\text{max}}$) when compared to the pretreatment values which reached the statistical significance. On the other hand, $V_{O_2}$ at 20% $P_{\text{max}}$, $V_{O_2\text{max}}$, HR, RER, and the blood lactate concentrations, as well as the $P_{\text{max}}$ were not different to the values obtained before the treatment.

There were no significant differences between the end of the treatment and 2 months after the end of the treatment for any of these parameters.

### 3.3. Carnitine and coenzyme A pools in the skeletal muscle

The carnitine pool in the skeletal muscle is shown in Table 3. The carnitine content could be determined in all eight subjects before the treatment, in seven subjects at the end of the treatment (insufficient tissue in one subject), and in six subjects 2 months after the termination of the treatment (two subjects refused the third biopsy). Regarding the radioenzymatic determination of the carnitine pool, none of the carnitine fractions assessed showed a significant increase during the treatment with L-carnitine. Although the skeletal muscle total carnitine content was in the average 17% higher after treatment with L-carnitine, this increase did not reach the statistical significance. Since the pools of free and acylcarnitines are variable according to the metabolic state of the skeletal muscle, the total carnitine content is the best marker for the skeletal muscle carnitine pool [9,12]. As shown in Fig. 2, at the end of treatment, the free carnitine content had increased in five but decreased in two individuals and the total carnitine content had increased in three and decreased in four individuals. Similar results were obtained for the analysis of the skeletal muscle specimens by HPLC (results not shown) and by in vitro NMR spectroscopy (Table 3). As shown in Fig. 3, the content of the free carnitine normalized to the total creatine by NMR spectroscopy showed a good correlation with the free carnitine content determined by the radioenzymatic method. The positive intercept in Fig. 3 should be mentioned. It indicates that the trimethylammonium peak of carnitine, as determined in the current experimental setup, overlapped with proton resonances of the other compounds (probably choline containing metabolites). There was no significant correlation between the skeletal muscle carnitine content and the body oxygen consumption, exercise performance or composition of skeletal muscle (data not shown).

The coenzyme A pool (free coenzyme A, acetyl-CoA, total acid soluble CoA, long-chain acyl-CoA, and total CoA) was not affected by treatment with L-carnitine (results not shown).

### Table 4

<table>
<thead>
<tr>
<th>Activity of mitochondrial enzymes</th>
<th>Before treatment $(n=8)$</th>
<th>End of treatment $(n=8)$</th>
<th>2 months after end of treatment $(n=6)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate synthase</td>
<td>$8.4 \pm 4.0$</td>
<td>$7.2 \pm 2.1$</td>
<td>$6.2 \pm 4.2$</td>
</tr>
<tr>
<td>Cytochrome oxidase</td>
<td>$3.4 \pm 1.4$</td>
<td>$3.1 \pm 1.1$</td>
<td>$4.5 \pm 1.3$</td>
</tr>
</tbody>
</table>

Healthy subjects $(n=8)$ were treated with oral L-carnitine $(2 \times 2 \text{ g/day for 3 months})$. Enzyme activities were determined spectrophotometrically in muscle biopsies obtained at rest before, immediately after, and 2 months after the treatment. Units are U/g muscle wet weight. Data are presented as the mean ± S.D. No significant differences between the different time point could be detected.
3.4. Enzyme activities

As shown in Table 4, in comparison to the values before the treatment, the activities of the citrate synthase and cytochrome oxidase were not increased immediately after the treatment, as well as 2 months after stopping the treatment with L-carnitine. These data are in agreement with the unchanged values for VO₂max obtained in the exercise performance tests at the same time points.

3.5. Skeletal muscle fiber composition

The skeletal muscle fiber type composition did not change during the treatment with L-carnitine. The percentage of type I fibers before the treatment was 53.9 ± 9.2%, at the end of the treatment 49.2 ± 6.3%, and 2 months after the end of the treatment 53.4 ± 10.4% (no significant difference between these values). These results agree well with the unaltered activity of the mitochondrial enzymes determined at the same time points.

4. Discussion

Despite the expected increase in the plasma carnitine concentration and urinary carnitine excretion, our studies demonstrated that the skeletal muscle carnitine content does not increase significantly during the long-term administration of a high daily dose of L-carnitine to moderately trained human subjects. Similar findings were recorded after the administration of a single intravenous dose of L-carnitine to human subjects [23] or after the administration of lower oral doses (2 g/day) to athletes over 4 months [32]. The compliance of the subjects has been monitored precisely and a technical problem in the determination of carnitine is very unlikely. The radioenzymatic assay used is a standard method, which has been described and validated in detail [37]. The results obtained by in vitro NMR spectroscopy are in close agreement with those obtained by the radioenzymatic method, leading to the same conclusions. Importantly, in vitro NMR spectroscopy allows for the determination of creatine and phosphocreatine in the same sample. As the total creatine content of the skeletal muscle is not expected to vary much with time, it can be used to normalize the carnitine content, eliminating all quantification inaccuracies involved in the work up of the muscle biopsies. The skeletal muscle carnitine content could be normalized to the total creatine content, excluding potential disturbances by alterations in the skeletal muscle composition. Similar to the carnitine pool, the coenzyme A pool was also not affected by the treatment with L-carnitine.

In humans, hydroxylation of butyrobetaine, the final step in the biosynthesis of carnitine [44], only occurs in the liver, kidney, brain, and possibly testes but not the skeletal muscle [45]. Thus, the carnitine requirements of the skeletal muscle must be met entirely by importing the carnitine from plasma. Since the carnitine concentration in the skeletal muscle is approximately 50 times higher than in the plasma (this study and Ref. [12]), the transport of carnitine into the skeletal muscle must be an active process. In studies using the muscle strips [46], cultured muscle cells [47], or skeletal muscle plasma membrane vesicles [48], active transport of the carnitine could be demonstrated, with a Km in the range of 10–20 μmol/l. A sodium-dependent carnitine carrier (OCTN2) with a high expression in the skeletal muscle and heart, exhibiting a Km of 4.3 μmol/l, has recently been cloned from a human kidney cell line [49]. Since the free carnitine concentration in the plasma is in the range of 30–40 μmol/l in normal individuals (Ref. [12] and this study), OCTN2 and the other potential carnitine transporters are saturated under normal conditions. In individuals with a normal plasma carnitine concentration, an increase in the plasma carnitine concentration is therefore not expected to lead to a higher carnitine uptake by the skeletal muscle.

A low affinity transport system for carnitine has been described in the cultured muscle cells [47] and rat kidney [50] which has a Km in the millimolar range. This transport system could therefore theoretically account for an increase in the carnitine transport into the skeletal muscle at high carnitine plasma concentrations, as observed during the treatment with L-carnitine. Since the skeletal muscle carnitine content did not increase in the subjects studied, despite the increased plasma carnitine concentrations, our investigations indicated that such transport system is quantitatively not important in humans with normal carnitine homeostasis.

A third possibility, how carnitine can reach the skeletal muscle, is by diffusion [48]. This possibility
can be excluded in normal subjects, since the skeletal muscle carnitine concentration is much higher than its concentration in plasma (this study and Ref. [12]). In agreement with this concept, intravenous administration of high doses of L-carnitine led to plasma concentrations in the millimolar range but was not associated with an increase in the carnitine skeletal muscle pool [23]. However, in patients with carnitine deficiency, who can have extremely low carnitine tissue levels [3,4], diffusion may be an important mechanism by which carnitine is transported to the tissues such as the skeletal muscle and heart.

Based on the in vitro observations of Brass et al. [14], an increase in the physical performance could be expected, if it were possible to increase the skeletal muscle carnitine pool. In apparent agreement with this observation, several studies in humans have shown an increase in the physical performance and/or a decrease in the respiratory exchange ratio after a single [17,18] or multiple doses of L-carnitine [16,19]. On the other hand, in other studies, no beneficial effect on these parameters could be detected after a single [23,25] or multiple doses of L-carnitine in human subjects [20–22,24]. In agreement with these latter studies, our investigations also revealed no significant changes in P\textsubscript{max}, \textit{V}O\textsubscript{2}\textsubscript{max}, and RER\textsubscript{max}. Also, in the submaximal range, no physiologically meaningful alterations in \textit{V}O\textsubscript{2}, \textit{V}CO\textsubscript{2}, or RER did occur. Regarding the results of the exercise tests, it is important to realize that the intra-individual variability was small. This excludes the technical problems or effects of learning, which would be expected to lead to an increase in the working capacity over time. The results of the exercise tests are in agreement with the biochemical studies, both showing no significant alterations associated with the long-term L-carnitine treatment.

Previous studies in marathon runners have shown that oral administration of 2 g of L-carnitine for 1 month was associated with increased activities of pyruvate dehydrogenase and complex I, III, and IV (cytochrome oxidase) of the respiratory chain but not of the citrate synthase or carnitine palmitoyltransferase I or II [30,31]. Our studies revealed no increase in the activities of the citrate synthase or cytochrome oxidase, excluding the proliferation of the skeletal muscle mitochondria in our subjects. In support of this interpretation, no increase in \textit{V}O\textsubscript{2}\textsubscript{max} was also detected, which is typically associated with the mitochondrial proliferation in the skeletal muscle [51]. As shown by the analysis of the muscle fibers, there was no increase in type I (oxidative) fibers, which could also have explained a higher activity of mitochondrial enzymes. While our studies clearly show that the long-term administration of L-carnitine to healthy, moderately trained volunteers is not associated with the proliferation of the skeletal muscle mitochondria and/or changes in the composition of the muscle fiber types, we cannot exclude that this may be different in highly trained subjects such as marathon runners.

In conclusion, the long-term oral administration of L-carnitine to moderately trained human subjects is neither associated with a significant increase in their skeletal muscle carnitine content nor with an increase in their physical performance. Beneficial effects of the long-term treatment with L-carnitine on the physical performance of healthy adults cannot be therefore explained by an increase in their carnitine skeletal muscle stores.

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