Supplemental carnitine and exercise[1–3]

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ABSTRACT Carnitine is an endogenous compound with well-established roles in intermediary metabolism. An obligate for optimal mitochondrial fatty acid oxidation, it is a critical source of energy and also protects the cell from acyl-CoA accretion through the generation of acylcarnitines. Carnitine homeostasis is affected by exercise in a well-defined manner because of the interaction of the carnitine-acylcarnitine pool with key metabolic pathways. Carnitine supplementation has been hypothesized to improve exercise performance in healthy humans through various mechanisms, including enhanced muscle fatty acid oxidation, altered glucose homeostasis, enhanced acylcarnitine production, modification of training responses, and altered muscle fatigue resistance. Available experimental clinical studies designed to assess the effect of carnitine on exercise metabolism or performance in healthy humans do not permit definitive conclusions to be drawn. In the aggregate, however, these studies suggest that carnitine supplementation does not improve maximal oxygen uptake or metabolic status during exercise in healthy humans. Carnitine administration for ≤1 mo in humans increases plasma carnitine concentrations but does not increase muscle carnitine content. Additional clinical trials integrating physiologic, biochemical, and pharmacologic assessments are needed to definitively clarify any effects of carnitine on exercise performance in healthy persons. *Am J Clin Nutr* 2000;72(suppl):618S–23S.

KEY WORDS Carnitine, acylcarnitine, muscle metabolism, exercise, respiratory quotient, oxygen consumption, athletic performance

INTRODUCTION

Carnitine (L-3-hydroxytrimethylamminobutanoate) is an endogenous compound with well-established functions in intermediary metabolism. Biological reactions involving carnitine can be described as follows:

$$\text{Carnitine} + \text{acyl-CoA} \rightleftharpoons \text{acylcarnitine} + \text{CoA} \qquad (1)$$

in which activated carboxylic acids (acyl groups) are reversibly transferred between coenzyme A and carnitine (1). Thus, the acylcarnitines and acyl-CoAs represent a spectrum of different compounds with specific acyl moieties (eg, acetylcarnitine is an example of a specific acylcarnitine).

Through the reaction shown above, carnitine is an obligate for optimal mitochondrial fatty acid oxidation. The inner mitochondrial membrane is impermeable to long-chain fatty acyl-CoAs (the term *long-chain* refers to carbon chain lengths of ≥10; short-chain refers to acyl groups of <10 carbons), and thus the activated fatty acids cannot reach the intramitochondrial site of β-oxidation. Long-chain acylcarnitines generated from the acyl-CoAs can transit the mitochondrial membrane, regenerating the acyl-CoAs in the mitochondrial matrix, where they are available as substrates for oxidation.

A second broad function of carnitine involves the formation of acylcarnitines from short-chain acyl-CoAs. The generation of the acylcarnitine serves to buffer the small, dynamic coenzyme A pool against metabolic transients and protects against acyl-CoA accumulation, which may be deleterious to cellular function (2).

The transfer of acyl groups between carnitine and coenzyme A appears to be near equilibrium in mammalian tissues. As a result, metabolic changes or transitions that occur in the critical coenzyme A pool are reflected in the carnitine pool (2, 3). The distribution of carnitine between carnitine and acylcarnitines, as well as the specific acyl groups in the acylcarnitine pool, has proven to be a useful research and clinical tool in assessing metabolism. Thus, an assessment of carnitine status in a biological compartment requires knowledge of not only the total carnitine content but also the relative amounts of carnitine and of short- and long-chain acylcarnitines.

CARNITINE HOMEOSTASIS IN HUMANS

Carnitine in humans is derived from both dietary sources and endogenous biosynthesis. Meat and dairy products are major dietary sources of this compound (4). Lysine provides the biosynthetic precursor for carnitine's carbon backbone, with the final steps of synthesis occurring in the liver and kidney (5). Irreversible loss of carnitine from humans is through urinary excretion of carnitine and acylcarnitines. Carnitine and acylcarnitines are both filtered and reabsorbed in the renal tubule with a transport maximum for reabsorption (6).

Substantial compartmentalization of carnitine pools occurs in humans, and there are tissue-specific differences in carnitine homeostasis. Carnitine and acylcarnitine are transported into cells via specific, saturable transport systems. Tissue carnitine export transport systems have also been identified, as have intracellular-extracellular carnitine-acylcarnitine exchange transport

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systems. Tissues differ in their complement of these transport systems (7), and thus there are differences in tissue carnitine contents, turnover rates, and metabolic availability. A comparison of total carnitine contents (the sum of carnitine and all acylcarnitines) in plasma (60 μmol/L), liver (900 μmol/kg), and skeletal muscle (4000 μmol/kg) illustrates these differences.

CARNITINE METABOLISM DURING EXERCISE IN HEALTHY SUBJECTS

Metabolic status during exercise can be classified as low intensity (below the individual's lactate threshold) or high intensity (above this threshold) (8). At low work rates, the respiratory quotient remains low, lactate does not accumulate, and exercise can be sustained. In contrast, at high work rates (above the lactate threshold), the respiratory quotient may be ≥1.00, lactate accumulates in muscle and blood, and subjects become rapidly fatigued.

This low- versus high-intensity paradigm allows evaluation of carnitine metabolism during exercise. At rest, the skeletal muscle carnitine pool is distributed as ≈80–90% carnitine, 10–20% short-chain acylcarnitine, and <5% long-chain acylcarnitine (9). Exercise for 60 min at low intensity has no effect on the skeletal muscle carnitine pool. However, after only 10 min of high-intensity exercise, the muscle carnitine pool is redistributed to ≈40% carnitine and 60% short-chain acylcarnitine (9, 10). This redistribution is accentuated over a further 20 min of exercise and does not fully normalize over a 60-min recovery period (9). In contrast with these dramatic shifts in the muscle carnitine pool, only minimal changes are seen in the plasma or urine carnitine pools.

Further insights into the metabolic changes that take place when a person moves from low- to high-intensity exercise are gained by examining the specific acyl moiety present in the muscle acylcarnitine pool. In healthy persons, acetylcarnitine is the dominant acylcarnitine present in the skeletal muscle during high-intensity exercise (11, 12). As predicted based on the equilibration of the carnitine and coenzyme A pools, acetyl-CoA increases in parallel to the accumulation of acetylcarnitine (11). Thus, the acetylcarnitine accumulation provides a window into the muscle's intermediary metabolism. The accumulation of acetyl-CoA suggests a mismatch between acetyl-CoA production and entry into the tricarboxylic acid cycle for complete oxidation. This model is also consistent with the association between acylcarnitine and lactate accumulation, because acetyl-CoA accumulation will inhibit pyruvate dehydrogenase activity.

PHARMACOKINETICS OF SUPPLEMENTAL CARNITINE IN HUMANS

The pharmacokinetics of carnitine are complex as a result of the diverse homeostatic mechanisms discussed above. From several features of carnitine's pharmacokinetics, it can be predicted that oral carnitine supplementation would have little, if any, affect on muscle carnitine content in humans. If given orally, carnitine has a systemic bioavailability of 5–15% (13, 14). Once in the systemic circulation, carnitine is rapidly distributed into a central compartment with a volume of distribution similar to the extracellular volume (15, 16). If plasma carnitine concentrations exceed the renal reabsorbtion maximum (equivalent to ≈60–100 μmol carnitine/L in plasma), the excess carnitine is eliminated in the urine with a clearance approximating the glomerular filtration rate (15, 17, 18). Thus, after acute administration of large doses of carnitine, most of the dose is rapidly recovered in the urine (15).

Carnitine can also move from the plasma into tissue compartments after carnitine dosing. The physiologic volume of distribution of carnitine is extremely large because of the sequestration of carnitine in muscle. Carnitine distributes into tissues with a distribution half-life of 2–3 h (19, 20). However, not all tissues are affected in an equivalent manner, and muscle is particularly refractory to acute supplementation because of its slower net turnover (15). Exogenous carnitine may still interact with the skeletal muscle carnitine pool without net uptake through plasma membrane carnitine-acylcarnitine exchange (21, 22), but the functional consequences of such an interaction are unknown. These observations have significant implications for therapeutic strategies predicated on achieving an increase in total muscle carnitine content.

The total body content of carnitine in healthy humans has been estimated as ≈20 g, or ≈120 mmol (20). Thus, given the low oral bioavailability and large renal losses after supplementation, very large dosing requirements for an extended period would be necessary to significantly affect carnitine muscle stores in healthy subjects.

Finally, it is important to note that serious questions have been raised about over-the-counter carnitine preparations available to consumers for supplementation. In a study of 12 over-the-counter carnitine formulations, the actual mean carnitine content was only 52% of that indicated on the label (23). Furthermore, 5 of 12 preparations had unsatisfactory pharmaceutical dissolution characteristics under careful evaluation (23). Bioavailability data are available only for the pharmaceutical-grade products, and comparative data are not available between products.

RATIONALE FOR CARNITINE SUPPLEMENTATION TO IMPROVE EXERCISE PERFORMANCE IN HEALTHY HUMANS

The relation between the muscle carnitine pool and critical bioenergetic pathways has led to speculations concerning the benefits of supraphysiologic carnitine concentrations in healthy humans. Various specific mechanisms have been postulated for a carnitine effect on exercise performance (**Table 1**).

Carnitine's obligatory role in mitochondrial fatty acid oxidation suggests that carnitine supplementation might increase fatty acid oxidation, thus making more ATP available for mechanical work (24). If carnitine administration increases muscle fatty acid oxidation, this might also delay the use of muscle glycogen and thus delay fatigue development (25). However, no evidence is available to show whether muscle carnitine content is rate limiting for fatty acid oxidation. Furthermore, because of the pharmacokinetic considerations above, it is not clear whether a

TABLE 1
Potential mechanisms for a beneficial effect of carnitine supplementation on exercise performance in healthy humans

- Enhance muscle fatty acid oxidation
- Decrease muscle glycogen depletion rates
- Shift substrate used in muscle from fatty acid to glucose
- Replace muscle carnitine redistributed into acylcarnitine
- Activate pyruvate dehydrogenase via lowering of acetyl-CoA content
- Improve muscle fatigue resistance
- Replace carnitine lost during training

TABLE 2
Effect of carnitine supplementation on exercise performance[1]

Study	Population	Daily carnitine dose	Treatment duration	Endpoints	Carnitine effects
Marconi et al, 1985 (25)	6 competitive walkers	4 g orally	2 wk	$\dot{V}O_2$max, lactate, RQ	Increase in $\dot{V}O_2$max, no change in RQ at fixed workload
Greig et al, 1987 (32)	9 untrained subjects	2 g orally	14 d	Maximal exercise, lactate	No change in $\dot{V}O_2$max or lactate
Greig et al, 1987 (32)	10 untrained subjects	2 g orally	28 d	Maximal exercise, lactate	No change in $\dot{V}O_2$max or lactate
Dragan et al, 1987 (43)	40 elite athletes	3 g orally	21 d	$\dot{V}O_2$max	Increase in $\dot{V}O_2$max
Oyono-Enguelle et al, 1988 (36)	10 untrained males	2 g orally	28 d	$\dot{V}O_2$, $\dot{V}CO_2$, RQ, lactate, plasma glucose at fixed workload exercise	No effect of carnitine
Soop et al, 1988 (37)	7 moderately trained males	5 g orally	5 d	FFA turnover during exercise, $\dot{V}O_2$ at fixed workload exercise	No effect of carnitine
Gorostiaga et al, 1989 (24)	10 trained athletes	2 g orally	28 d	RQ, $\dot{V}O_2$, heart rate, lactate, plasma glucose at fixed workload	Decrease in RQ; no other significant changes
Siliprandi et al, 1990 (41)	10 moderately trained males	2 g orally	1 dose 1 h before exam	Plasma lactate	Postexercise lactate reduced by carnitine
Vecchiet et al, 1990 (42)	10 moderately trained males	2 g orally	1 dose 1 h before exercise	$\dot{V}O_2$max, plasma lactate	$\dot{V}O_2$max increased and lactate decreased
Wyss et al, 1990 (33)	7 healthy males	3 g orally	7 d	$\dot{V}O_2$max RQ	No effect of carnitine under normal conditions
Decombaz et al, 1993 (38)	9 healthy males	3 g orally	7 d	Fat oxidation, RQ, perceived exertion, lactate, heart rate during exercise after glycogen depletion	No effect of carnitine
Natali et al, 1993 (44)	12 active males	3 g intravenously	1 dose 40 min before exercise	$\dot{V}O_2$, $\dot{V}CO_2$, substrate oxidation during and after exercise	No changes during exercise, but increased fatty acid oxidation during recovery with carnitine
Trappe et al, 1994 (34)	20 male athletes	2 g BID orally	7 d	Swimming performance, lactate concentration	No effect of carnitine
Brass et al, 1994 (15)	14 healthy males	92.5 mol/kg or 18.5 mol/kg intravenously	1 dose at beginning of exercise	RQ, $\dot{V}O_2$ lactate, muscle glycogen at fixed workload	No effect of carnitine
Vukovich et al, 1994 (39)	8 healthy males	6 g orally	7–14 d	RQ, FFA glucose utilization, $\dot{V}O_2$ during fixed workload exercise	No effect of carnitine
Barnett et al, 1994 (40)	8 healthy males	4 g orally	14 d	Lactate during exercise, muscle carnitine content	No effect of carnitine
Colombani et al, 1996 (35)	7 male athletes	4 g orally	Day of event	Marathon time and postrace lactate	No effect of carnitine

[1] BID, twice daily; FFA, free fatty acids; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_2$ max, maximal oxygen consumption during exercise; RQ, respiratory quotient ($\dot{V}CO_2/O_2$).

significant change in muscle carnitine content will result from carnitine supplementation.

In contrast with the idea of accelerating fatty acid oxidation by carnitine supplementation, data from animal heart models suggest that exogenous carnitine can induce an increase in glucose oxidation at the expense of fatty acid oxidation (26). A shift in the fuel substrate mix to glucose allows more ATP generation per O_2 consumption (8). This factor may be important in ischemic conditions, but its relevance to healthy humans is unclear. The mechanism of carnitine-induced enhanced glucose oxidation may involve activation of pyruvate dehydrogenase secondary to reductions in acetyl-CoA content as acetylcarnitine is generated (27). Activation of pyruvate dehydrogenase would facilitate complete glucose oxidation and minimize lactate accumulation. However, the close equilibrium between acetyl-CoA and acetylcarnitine in vivo (11) makes it difficult to envision sustained transfer of acetyl groups from the coenzyme A to carnitine pools. Demonstration of carnitine effects on pyruvate dehydrogenase requires maximizing acetyl-CoA's inhibitory effect on the enzyme (28).

Carnitine content in skeletal muscle falls during high-intensity exercise as acylcarnitines accumulate (9). Thus, carnitine availability might become rate limiting even if baseline values are adequate. Again, no data are available to support this postulate, nor is it clear that supplemental carnitine would overcome any limitation. Muscle carnitine content has been reported to decrease with exercise training (29), but the functional significance of this change or its prevention via supplementation cannot be predicted.

Impairment of muscle contractility due to fatigue may play a role in determining human performance. Through unclear mechanisms, high carnitine concentrations were shown to delay muscle fatigue and permit improved maintenance of contractile force in studies using in vitro animal systems (30, 31). The relevance of these observations to human exercise is unknown.

TABLE 3
Effect of carnitine supplementation on aerobic training

Study	Population	Daily carnitine dose	Treatment duration	Endpoints	Carnitine effects
Arenas et al, 1991 (29)	24 athletes	2 g orally	6 mo training	Muscle carnitine content	Prevent training-associated decrease in muscle carnitine
Huertas et al, 1992 (45)	14 athletes	4 g orally	4 wk training	Mitochondrial electron transport chain enzyme activities	Increase in enzyme activities with carnitine
Arenas et al, 1994 (46)	16 long-distance runners	2 g orally	4 wk training	Muscle pyruvate dehydrogenase and carnitine palmitoyltransferase activity	Increased pyruvate dehydrogenase but no change in carnitine palmitoyltransferase activity

EFFECT OF CARNITINE SUPPLEMENTATION ON EXERCISE PERFORMANCE IN HEALTHY HUMANS

Published studies of carnitine supplementation to modify exercise performance in healthy humans are summarized in **Tables 2** and **3**. Only studies designed to examine carnitine's actions as an adjunct to training are shown in Table 3. In reviewing the body of literature the reader should carefully differentiate the design features of the various studies. Administration of carnitine has varied with respect to route, dose, and duration of treatment; each of these dosing parameters could substantially affect any pharmacologic benefit of carnitine. In addition, the studies involved populations that were diverse in athletic experience, age, and sex. Study endpoints were either performance based [eg, maximal oxygen uptake ($\dot{V}O_2$max), athletic performance, or perceived exertion] or metabolic surrogates (eg, respiratory quotient, lactate accumulation, or oxygen consumption at a fixed work rate). This diversity in design makes consensus difficult to extract from the clinical trials of carnitine use in healthy subjects. It is beyond the scope of this review to critically examine each study in detail; instead, points of relative agreement or clear controversy will be emphasized.

Most studies in which exercise capacity was studied with use of either $\dot{V}O_2$max or performance endpoints failed to show any benefit of carnitine supplementation when the duration of therapy ranged from acute administration to 1 mo (32–35). Similarly, attempts to modify exercise metabolic indexes usually failed to identify any effect of carnitine supplementation (15, 36–40). Exceptions have been reported, however. Specifically, carnitine was found to reduce exercise-associated lactate accumulation (41, 42), to increase $\dot{V}O_2$max (25, 42, 43), and to enhance fatty acid oxidation (44). Yet, the few positive results are in many ways difficult to comprehend given our understanding of carnitine homeostasis. As discussed above and as emphasized by Hultman et al (47), it is unlikely that carnitine supplementation over a period of days to weeks will change muscle total carnitine content in humans. Available data confirm that muscle carnitine content is not increased by supplementation protocols similar to those described above (15, 39, 40), despite increases in plasma carnitine concentrations (15, 34, 39, 40, 44). Thus, although it is possible that carnitine affects exercise physiology without modifying muscle carnitine pools, such a mechanism would clearly be distinct from the rationales for supplementation introduced previously. Note that increases in muscle carnitine content might result from longer durations of therapy or if muscle carnitine homeostasis is distributed.

Work by Arenas et al (29, 45, 46) provides evidence for a distinct effect of carnitine (Table 3). Importantly, the work by Arenas et al examined only athletes engaged in training programs for periods of 1–6 mo. Under these conditions, carnitine supplementation prevented a training-associated decrease in muscle carnitine content and also increased muscle activity of key oxidative enzymes, including pyruvate dehydrogenase and electron transport chain enzymes. However, the physiologic effect of these changes is unknown and further corroboration of these findings is needed.

Finally, it is important to note that carnitine supplementation may benefit exercise performance in disease states. Patients with chronic renal failure (48) and peripheral vascular disease (49) have been reported to increase their exercise capacity after treatment with carnitine. In both conditions, muscle carnitine content was shown to be increased with long-term supplementation, although the specific mechanism for any effects of carnitine in these disorders has not been defined. Carnitine supplementation has also been suggested to be beneficial in treating chronic fatigue syndrome (50).

CONCLUSIONS AND CONSIDERATIONS FOR FUTURE WORK

Carnitine is an endogenous compound with well-established functions in cellular metabolism that are clearly important in muscle during exercise. Muscle carnitine homeostasis is perturbed during exercise, and theoretical bases exist for carnitine supplementation to improve exercise function in healthy humans. However, the endogenous carnitine pool may be adequate for metabolic needs, and the muscle pool is refractory to perturbation from exogenous carnitine. In contrast with data in disease states, the preponderance of experimental data suggest that carnitine supplementation does not modify exercise performance in healthy humans.

The negative data available to date may not be definitive with respect to carnitine's effect on exercise performance because of study design limitations. Future studies should include adequately powered, placebo-controlled clinical trials examining physiologically relevant endpoints including $\dot{V}O_2$max, $\dot{V}O_2$ at defined work rates, and the lactate threshold $\dot{V}O_2$. Subject populations should be carefully defined to differentiate athletes from nonathletes and should identify individuals engaged in training programs. Any sex differences in carnitine effects also remain undefined. To maximize interpretation of results, studies should collect and integrate data on carnitine's pharmacology (ie, dose, duration of treatment, and relation of carnitine concentration to effect) with biochemical effects (ie, substrate and intermediate fluxes) and physiologic responses. Duration of carnitine treatment may be a particularly critical variable, given carnitine's pharmacokinetics and the long durations of treatment associated with benefit in disease states (48, 49) or with training (29). Such data will not only definitively address the question of the role of carnitine supplementation but

will also provide important insights into the regulation of metabolism during exercise in humans.

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