Review Article

The Role of Carnitine and Carnitine Supplementation During Exercise in Man and in Individuals with Special Needs

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Carnitine is critical for normal skeletal muscle bioenergetics. Carnitine has a dual role as it is required for long-chain fatty acid oxidation, and also shuttles accumulated acyl groups out of the mitochondria. Muscle requires optimization of both of these metabolic processes during peak exercise performance. Theoretically, carnitine availability may become limiting for either fatty acid oxidation or the removal of acyl-CoAs during exercise. Despite the theoretical basis for carnitine supplementation in otherwise healthy persons to improve exercise performance, clinical data have not demonstrated consistent benefits of carnitine administration. Additionally, most of the anticipated metabolic effects of carnitine supplementation have not been observed in healthy persons. The failure to demonstrate clinical efficacy of carnitine may reflect the complex pharmacokinetics and pharmacodynamics of carnitine supplementation, the challenges of clinical trial design for performance endpoints, or the adequacy of endogenous carnitine content to meet even extreme metabolic demands in the healthy state.

In patients with end stage renal disease there is evidence of impaired cellular metabolism, the accumulation of metabolic intermediates and increased carnitine demands to support acylcarnitine production. Years of nutritional changes and dialysis therapy may also lower skeletal muscle carnitine content in these patients. Preliminary data have demonstrated beneficial effects of carnitine supplementation to improve muscle function and exercise capacity in these patients.

Peripheral arterial disease (PAD) is also associated with altered muscle metabolic function and endogenous acylcarnitine accumulation. Therapy with either carnitine or propionylcarnitine has been shown to increase claudication-limited exercise capacity in patients with PAD.

Further clinical research is needed to define the optimal use of carnitine and acylcarnitines as therapeutic modalities to improve exercise performance in disease states, and any potential benefit in healthy individuals.

Key teaching points:

- Carnitine is required for mitochondrial fatty acid oxidation and to minimize the impact of cellular acyl-CoA accumulation.
- The pharmacokinetics of carnitine are complex due to low oral bioavailability, complex distribution between tissues, intracconversion to acylcarnitines and saturable renal transport systems.
- Theoretically, carnitine supplementation may increase carnitine content, increase fatty acid oxidation and protect from the accumulation of metabolic intermediates.
- Clinical trials do not support the use of carnitine supplementation to improve exercise performance in healthy man.
- End-stage renal disease and peripheral arterial disease are both associated with exercise impairment and metabolic alterations which are improved by carnitine supplementation.

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INTRODUCTION

The determinants of human exercise performance are multifactorial and complex. The performance of skeletal muscle work during exercise is dependent on the availability of biochemical energy in the form of ATP. Thus, it is not surprising that a variety of metabolic and biochemical markers are related to exercise performance and training [1,2] or that disorders of energy metabolism are frequently associated with impaired exercise performance [3]. Similarly, manipulations of bioenergetics have frequently been proposed as strategies to enhance exercise endurance or capacity.

Carnitine is an endogenous molecule with well established important roles in cellular metabolism [4]. The functions of carnitine in skeletal muscle are critical to sustaining normal bioenergetics during exercise. All biochemical actions of carnitine are based on the carnitine acyltransferase-mediated reversible transfer of carboxylic acids, or “acyl” groups, between carnitine and coenzyme A in reactions of the following form:

\[
\text{Carnitine} + \text{Acyl-CoA} \leftrightarrow \text{Acylcarnitine} + \text{Coenzyme A}
\]

Coenzyme A is an important cofactor in a number of catabolic and anabolic reactions. Thus the carnitine pool, consisting of carnitine, short-chain acylcarnitines (acylcarnitines corresponding to short- and medium-chain length carboxylic acid groups), and long-chain acylcarnitines (corresponding to long-chain length carboxylic acid), will dynamically interact with multiple coenzyme A-dependent biochemical pathways.

Carnitine is required for mitochondrial long-chain fatty acid oxidation [4], a major source of energy during exercise [5]. Long-chain acylcarnitines transport activated long-chain fatty acids into the mitochondrial matrix for β-oxidation. Short-chain acylcarnitines are generated from short-chain acyl-CoAs. This generation of short-chain acylcarnitines may be viewed as buffering the cellular coenzyme A pool from acyl-CoA accretion, as accumulation of short-chain acyl-CoAs may adversely affect cellular metabolism [6]. The reversible transfer of short-chain acyl groups between carnitine and coenzyme A occurs dynamically in muscle during exercise. For example, acetyl-carnitine accumulation in muscle at workloads above the lactate threshold [8–10] corresponds to the accumulation of acetyl-CoA in the muscle [11].

The important biochemical functions of carnitine and the altered muscle physiology associated with clinical carnitine deficiency [7] support the critical role of carnitine in muscle bioenergetics. However, the extrapolation of these established concepts to the effects of carnitine supplementation in healthy persons or in varied pathologic conditions is less clear. It is unknown whether supraphysiologic carnitine concentrations enhance exercise performance, or which pathophysiologic conditions might be associated with decreased muscle carnitine content or increased carnitine requirements.

The biochemistry [4,12], pharmacology [13,14] and exercise physiology [15–17] of carnitine have been recently reviewed. The current review is designed to focus on the concepts which form the basis for carnitine supplementation to improve exercise performance, and the most recent clinical data.

BIOCHEMICAL BASIS FOR CARNITINE SUPPLEMENTATION TO IMPROVE EXERCISE PERFORMANCE

The known biochemical or physiologic effects of carnitine suggest actions of supplemental carnitine that may improve exercise performance (Table 1). While these rationales are attractive, varied assumptions have often gone unchallenged and supportive data from clinical studies are frequently not available.

Carnitine is required for mitochondrial fatty acid oxidation, and thus it is reasonable to speculate that an increase in carnitine content might increase the rate of fatty acid oxidation. Such a hypothesis would be further supported by the decrease in muscle carnitine content which occurs during high-intensity exercise as acetylcarnitine is generated [8–10]. Maintaining the rate of fatty acid oxidation would permit glucose utilization to decrease [18], and thus preserve muscle glycogen content and ensure maximal rates of oxidative ATP production. Depletion of muscle glycogen has been linked to fatigue [19], and thus glycogen preservation might be inherently performance enhancing. However, it is not clear that muscle carnitine content ever becomes rate limiting for mitochondrial fatty acid oxidation in normal man, nor under what conditions it may be rate limiting in disease states.

Varied techniques have been used to assess the effect of carnitine administration on fatty acid oxidation. During steady state exercise below the lactate threshold the respiratory quotient reflects the relative rates of glucose and fat oxidation [5], and when combined with the rate of oxygen consumption can be used to estimate the absolute rate of fatty acid oxidation [20]. Carnitine supplementation by various strategies, ranging from administration immediately preceding the exercise evaluation to 4 weeks of oral administration, have failed to demonstrate any effect on the respiratory quotient during exercise [21–27] with one exception [28]. Additionally, Soop et al [24]...
Pyruvate will be converted to lactate if pyruvate dehydrogenase activity is inadequate. The removal of the acetyl group as acetylcarnitine via carnitine generation exceeds utilization in the tricarboxylic acid cycle, acetyl-CoA will accumulate and can inhibit pyruvate dehydrogenase (— in figure). Sustained for very brief periods in human muscle.

An alternative mechanism by which carnitine might be postulated to enhance exercise performance is through short-chain acylcarnitine production. The bioenergetic demands of exercise place extreme stresses on the metabolic machinery of the muscle. Acetyl-CoA is the common product of glycolysis and fatty acid β-oxidation, and is the substrate for subsequent complete oxidation in the tricarboxylic acid cycle (Fig. 1). If acetyl-CoA generation exceeds the capacity of utilization in the tricarboxylic acid cycle, the acetyl-CoA concentration will rise. Acetyl-CoA can inhibit pyruvate dehydrogenase, the enzyme which catalyzes the conversion of pyruvate to acetyl-CoA [37]. Under conditions of inadequate pyruvate dehydrogenase activity to meet the rate of pyruvate formation, lactate is produced from the pyruvate. This linked accumulation of lactate and acetyl-CoA is observed in the muscle of man during high-intensity exercise [11].

Formation of acetylcarnitine from acetyl-CoA may represent an alternative product of oxidation. Generation of acetylcarnitine would potentially decrease acetyl-CoA content, relieving inhibition of pyruvate dehydrogenase and making coenzyme A available, as well as bypassing the apparent rate limitation of acetyl-CoA entry into the tricarboxylic acid cycle.

The potential importance of acetylcarnitine formation on mitochondrial oxidation has been demonstrated in vitro. Addition of carnitine to isolated mitochondria can decrease mitochondrial acetyl-CoA content [32] and increase flux through pyruvate dehydrogenase [33]. However, demonstration of these effects is dependent on a variety of potentially non-physiologic conditions, including high carnitine concentrations, non-steady state conditions permitting sustained flux towards acetylcarnitine, and the inhibition of alternative pathways for acetyl-CoA utilization. Thus, in contrast to the above effects of carnitine, the addition of high carnitine concentrations has no effect on mitochondrial acetyl-CoA content in isolated liver mitochondria oxidizing palmitate at maximal rates [34]. Similarly, increasing the hepatic carnitine content several fold has no sustained effect on the hepatic acetyl-CoA content, as the system rapidly reaches equilibrium [35]. The carnitine-coenzyme A interaction also appears to be near equilibrium after exercise [60]. The importance of this latter point can be visualized in exercising muscle by relating the rate of acetyl-CoA generation to the amount of carnitine available for acetylcarnitine formation. The rate of flux through pyruvate dehydrogenase during exercise at near maximal workloads has been estimated as 1.9 mmol/minute per kg [36]. This rate of acetyl-CoA production, which excludes the substantive contribution from fatty acid oxidation, would convert the entire muscle carnitine pool (approximately 4 mmol/kg [8]) to acetylcarnitine in just 2 minutes. Thus, this system can respond to transient, but not sustained, disproportionate acetyl-CoA production. Further, the amount of carnitine needed to sustain net flux for an additional 2 minutes would require a doubling of muscle carnitine content.

Another tenant of the enhanced acetylcarnitine hypothesis is not also be relevant to muscle metabolism during exercise. While acetyl-CoA inhibition of pyruvate dehydrogenase can be readily demonstrated in vitro [37], this may not be relevant in vivo. During exercise, particularly at high-intensities, the activity of pyruvate dehydrogenase is disassociated from the acetyl-CoA content as well as from the ratio of the acetyl-CoA and coenzyme A concentrations [11,36]. Thus, even if sustained net flux from acetyl-CoA to acetylcarnitine was obtained, it might not lead to enhanced flux through pyruvate dehydrogenase.

**Fig. 1.** The critical role of acetyl-CoA in oxidative metabolism. Both glucose and fatty acids yield acetyl-CoA which can enter the tricarboxylic acid cycle for complete oxidation. Pyruvate generated by glycolysis (①) from glucose generates acetyl-CoA via pyruvate dehydrogenase (②). If acetyl-CoA generation exceeds utilization in the tricarboxylic acid cycle, acetyl-CoA will accumulate and can inhibit pyruvate dehydrogenase (— in figure). Pyruvate will be converted to lactate if pyruvate dehydrogenase activity is inadequate. The removal of the acetyl group as acetylcarnitine via carnitine acetyltransferase (③) can remove this inhibition and produce an alternative product of oxidation. The net production of acetylcarnitine can only be sustained for very brief periods in human muscle.
Carnitine and Exercise

Muscle fatigue is a complex event which may involve metabolic, neural and psychologic components under different conditions\,\,[38,39]. In situ\,\,[40] and in vitro\,\,[41] studies have demonstrated that under some conditions exogenous carnitine can modify the loss of muscle contractile force with repetitive stimulation. These studies have been notable for the absence of consistent metabolic correlates to carnitine’s effect. The mechanism of these actions of carnitine and their relationship to in vivo muscle physiology are yet to be elucidated.

Studies of carnitine\,\,[42] and its acyl derivatives\,\,[43] have identified changes in blood flow which may affect tissue bioenergetics. The mechanism for these effects of carnitine and its derivatives are unclear and may be indirect. For example, carnitine may modify endothelial cell function\,\,[44], leading to changes in vascular dynamics. Again, the relevance of these observations to human physiology or exercise performance are unclear.

Thus, despite the logic of the arguments and the availability of some supportive data, the theoretical basis for carnitine’s efficacy in improving muscle function can be credibly challenged. Any conclusion on the beneficial effects of carnitine will depend on the availability of data from human clinical trials.

**CLINICAL TRIALS OF CARNITINE SUPPLEMENTATION**

**Methodologic Considerations**

It is important to recognize the challenges to studying carnitine’s effects in human exercise before considering specific studies. First, the method of carnitine administration must be defined. The oral bioavailability of carnitine is approximately 5 to 15\%\,\,[45,46]. Thus, only a fraction of the orally administered dose will reach the systemic circulation, in contrast to intravenous administration. The total body carnitine content in a 70 kg man has been estimated as 128 mmol or 20 g\,\,[14]. As a result, large amounts of oral carnitine are required to perturb the endogenous pools. Dosing of carnitine is further complicated by the availability of over-the-counter formulations with apparently low carnitine contents and poor dissolution properties\,\,[47]. Given the large size of the endogenous pools, the duration of carnitine supplementation becomes an important parameter in clinical trials. For example, if 10\% of the dose reaches the systemic circulation, and 4\% of the dose is excreted in the urine\,\,[46], oral dosing of 2 g per day will yield a net increase in the body pool of 0.12 g per day. Thus, 2 weeks of supplementation would increase the body pool by only 8\%. These numbers are only estimates, but illustrate the importance of the dosing parameters in carnitine clinical trials.

The study population in carnitine-exercise clinical trials has varied even when only “healthy” subjects are considered. The inclusion of sedentary adults, recreational athletes or elite athletes may yield very different responses given the distinct biochemistry and physiology of these populations. Similarly, superimposing a training regimen during the treatment period may not be equivalent to maintaining the subjects’ normal activity.

End-points for exercise studies must be chosen carefully, and these various possible end-points assess different aspects of exercise physiology and performance. Measurement of the maximal rate of oxygen uptake (VO$_{2\text{max}}$) provides a reproducible assessment of maximal exercise capacity\,\,[5]. The maximal rate of oxygen consumption may be limited by ventilatory, cardiac or peripheral muscle determinants\,\,[5] and is clearly a reflection of fundamental physiologic characteristics of the subject. Changes in VO$_{2\text{max}}$ occur with aerobic training and reflect alterations in the capacity to perform physical tasks. However, the relationships between VO$_{2\text{max}}$ and the ability to perform specific activities are complex. Thus, evaluations that assess performance at specific tasks, athletic activities or sustained endurance exercise regimens have been used in an attempt to provide more generalizable assessments. However these tasks are less reproducible than maximal exercise testing and are subject to influence by a variety of factors other than the underlying physiology or metabolic status of the subject.

A number of additional endpoints have been used in studies of carnitine supplementation, including muscle mass, muscle enzyme activities, muscle pain, respiratory quotient, oxygen consumption at fixed workload and substrate or metabolite concentrations. The relevance of these measures to human exercise performance are not clear. Thus, the clinical goals of carnitine supplementation must be explicitly considered when assessing the available clinical trials results.

As with any clinical trial, studies to define the effects of carnitine on exercise performance must have adequate statistical power to detect the anticipated changes. Similarly, appropriate controls must be available to provide confidence in any presumed drug effect. These considerations are particularly important in studies with physical performance end-points to avoid subjective influences in the measurements, and the intrinsic variability in the testing modalities.

Clinical trials of carnitine supplementation in healthy subjects have recently been reviewed\,[17]. Many of these studies have one or more design deficiencies in the context of the above discussions. In particular, oral carnitine dosage was frequently given for only 7 to 14 days, and in no case for more than 28 days\,[17]. Most studies included \(\leq\)ten subjects, and objective physiologic end-points such as VO$_{2\text{max}}$ were assessed in only a few studies.

Five publications (Table 2) report studies of the effect of carnitine on VO$_{2\text{max}}$. Three studies reported an increase in VO$_{2\text{max}}$\,[21,44,50] and two demonstrated no effect of carnitine\,[48,51]. The study of Vecchiet et al\,[50] demonstrated that a single dose of carnitine an hour before exercise increased VO$_{2\text{max}}$. As pointed out by Hultman et al\,[52], and consistent with the design considerations above, it is extremely difficult to understand the action of a single oral carnitine dose on muscle
metabolism or function. The studies of Marconi et al [21] and Dragan et al [49] utilized competitive athletes as subjects and demonstrated a positive effect of carnitine. The studies of Wyss et al [51], Greig et al [48], and Marconi et al [21] all used placebo-controlled, double blinded crossover designs. However, the washout period between carnitine and placebo treatments was short (1 to 2 weeks) or not specified, and it is unclear whether the statistical analysis examined for an order-effect on the crossover design. The positive study of Dragan et al [49] used a larger number of subjects in a placebo-controlled parallel design. However, the analysis was based on a increase in VO\textsubscript{2max} during treatment in the carnitine but not the placebo group. The change in VO\textsubscript{2max} with carnitine was not compared to the placebo response, as would have been appropriate in a placebo-controlled, double blinded crossover designs. Nonetheless, reports of carnitine effects have appeared [28,50,54]. All of these studies, both positive and negative, suffer from the dosage limitations discussed above. However, the absence of clear metabolic effects of carnitine supplementation support the conclusion that oral supplementation with carnitine for periods up to 4 weeks is unlikely to modify exercise performance in healthy persons. Consistent with this concept, use of carnitine administration to athletes to improve performance in specific activities such as competitive swimming or marathon running has not demonstrated benefits [55,56].

Arenas and colleagues have studied carnitine supplementation in competitive athletes engaged in training programs [57–59]. These studies utilized oral administration for periods of from 1 to 6 months. Arenas reported that training was associated with a decrease in muscle carnitine content that was prevented by carnitine supplementation [57]. Carnitine supplementation was also associated with increased activities of several muscle mitochondrial enzymes. No performance or exercise physiology end-points were included in these studies.

The current studies do not support the use of carnitine supplementation to enhance exercise performance in healthy man. However, due to design limitations, the studies available cannot be viewed as definitively negative. Future studies might benefit from long durations of supplementation (i.e., months), randomized, placebo-controlled, parallel design, and optimized performance end-points such as VO\textsubscript{2max}. Special conditions, such as training of athletes, might also merit particular attention.

### Carnitine Supplementation in Patients with End-Stage Renal Disease

Chronic renal failure is associated with a marked impairment in exercise performance which directly impacts the quality of life in patients with this disorder [61]. Additionally, patients with end-stage renal disease demonstrate a spectrum of metabolic abnormalities, including accumulation of acylcarnitines in plasma [62,63]. Endogenous carnitine homeostasis is perturbed by the loss of renal function, acylcarnitine accretion and potential chronic losses of carnitine during dialysis [64]. Muscle carnitine content is inversely correlated to the length of time patients have been on dialysis, and is directly correlated with VO\textsubscript{2max} in patients on maintenance hemodialysis [65].

These concepts have led to a number of relatively small trials using intravenous carnitine administration to improve skeletal muscle function in hemodialysis patients. Intravenous carnitine administration is very effective in increasing muscle total carnitine content in these patients [66,67] as the normal rapid renal elimination of the dose [26] does not occur. In a randomized, placebo-controlled trial, 20 mg/kg carnitine administered at the end of dialysis for 6 months resulted in an 11% increase in VO\textsubscript{2max} [68]. Unfortunately, exercise performance was a secondary end-point in this trial, and only a minority of patients entered into the study participated in the exercise evaluations. Nonetheless, other studies have also suggested that carnitine improves muscle structure and function in these patients, including a decrease in intradialytic muscle symptoms [68–71]. The exciting preliminary data in this population warrants the conduct of additional clinical studies of carnitine therapy in this severely debilitated population.

### Carnitine Supplementation in Patients with Peripheral Arterial Disease

Peripheral arterial disease (PAD) results from atherosclerotic lesions in the arteries of the lower extremity. Peripheral arterial disease is associated with severe limitations in exercise capacity secondary to ischemic pain in the muscle (termed claudication). Strong evidence indicates that the chronic ischemia of PAD results in multiple metabolic changes in the muscle of the leg [72,73], including an accumulation of acylcarnitines [73]. The metabolic sequelae of PAD appear to have direct functional significance [73,74].

Brevetti and colleagues [75] in a double-blinded, cross-over
Carnitine Supplementation for Other Clinical Disorders

In addition to the conditions discussed above, carnitine supplementation has been suggested to have efficacy based on exercise-related end-points in chronic fatigue syndrome [81], angina [82] and chronic lung disease [83]. The literature on these potential indications is insufficient to allow conclusions to be drawn, but illustrate the broad interest in carnitine supplementation to enhance physical performance.

SUMMARY

Carnitine has well established functions in muscle metabolism which are directly relevant to exercise performance. However, the impact of supraphysiologic carnitine availability in healthy persons may not improve muscle metabolism when contrasted with the normal endogenous pool. The regulation of the carnitine pool makes perturbation of the muscle pool with exogenous supplementation difficult. Clinical trials of carnitine supplementation have been inconclusive and suffer from a number of design limitations. Thus, available data do not support the use of carnitine supplementation to improve exercise performance in healthy persons.

In contrast, carnitine therapy may improve exercise capacity in patients with end stage renal disease or PAD. These disorders are associated with severe exercise limitation and metabolic derangement affecting the carnitine pool. Work in these disorders emphasizes the potential of carnitine therapy in conditions of metabolic dysfunction, and illustrates the importance of well-designed clinical trials in evaluating the potential efficacy of carnitine.

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Carnitine and Exercise


Carnitine and Exercise


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