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REVIEW

The effects of L-carnitine supplementation in athletic performance



Les effets d'un complément alimentaire en L-carnitine dans la performance sportive

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Summary

Objectives. – This review aims to analyze the available data, mainly the most recent, regarding L-carnitine supplementation and exercise performance, in order to understand if L-carnitine can still be considered an ergogenic supplement. Moreover, it also aims to briefly analyze other potential uses, more specifically the effects on weight loss, recovery after exercise and aging. **News.** – A literature search, using the online scientific databases PubMed and Scopus, was conducted to identify studies related to L-carnitine supplementation and athletic performance. The discovery that skeletal muscle carnitine content can be increased through oral supplementation in humans represented a significant progress in this area. More recently, due to this discovery, new research has been done to investigate whether L-carnitine supplementation could have an impact on fuel metabolism. However, the inconsistency of results led to a change in the focus of research, shifting towards the investigation of the impact L-carnitine could have on the process of recovery after exercise and on aging.

Prospects and projects. – In future research, this new area needs to be more explored. Nevertheless, the study of the L-carnitine supplementation impact on fuel selection during exercise should continue and it is crucial to use athletes.

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Des sports

Conclusion. – Despite some performance benefits have been demonstrated, more research needs to be done. Presently, the available data is still not enough to widely recommend the use of L-carnitine supplements with the aim of improving exercise performance.

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Résumé

Objectifs. – Cette revue a pour but d'analyser les données disponibles, principalement les plus récentes, concernant l'utilisation d'un complément alimentaire en L-carnitine et la performance sportive, afin de comprendre si la L-carnitine peut encore être considérée comme un complément ergogénique. En plus de cela, il vise également à analyser brièvement d'autres utilisations potentielles, plus spécifiquement les effets sur la perte de poids, la récupération après l'exercice et le vieillissement.

Actualités. – Une recherche documentaire, utilisant les bases de données électroniques PubMed et Scopus, a été menée pour identifier les études liées à compléments alimentaires en L-carnitine et à la performance sportive. La découverte que le teneur en L-carnitine dans le muscle squelettique peut être augmentée chez l'homme par voie orale constitue un progrès significatif dans ce domaine. Cependant, l'incohérence des résultats a entraîné une modification de l'objectif de la recherche, qui a commencé à examiner l'impact que la L-carnitine pouvait avoir sur le processus de récupération après l'exercice et sur le vieillissement.

Perspectives et projets. – Dans les études futures, ce nouveau domaine doit être exploré davantage exploré. Cependant, l'étude de l'impact d'un complément alimentaire en L-carnitine sur le substrat énergétique utilisé pendant l'exercice doit se poursuivre et il est essentiel que les études soient menées sur les athlètes.

Conclusion. – Malgré certains effets bénéfiques sur la performance sportive aient déjà été démontrés, d'autres études sont nécessaires. Les données disponibles ne sont pas encore suffisantes pour recommander largement l'utilisation de compléments alimentaires de L-carnitine afin d'améliorer les performances sportives.

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1. Introduction

The use of dietary supplements is very common not only among athletes, but also in the general population [1]. While athletes aim to improve their performance [1], the main reason for the use of dietary supplements in the general population is an overall health/wellness benefit [2]. More specifically, with regard to the use of L-carnitine supplements, a recent study with a group of Dutch competitive athletes found that 3.9% had taken L-carnitine supplements any time in the past and 2.1% had taken it in the four weeks prior to the study [3]. Besides, a study with subjects who exercise at a commercial gym found a 6.8% use of L-carnitine supplements in those who go to the gym regularly (greater than five times per week), 3.6% among the ones who go occasionally (two to four times per week) and a 6.3% use in subjects who go to the gym one or two times per week or less [4].

L-carnitine was discovered in 1905 when was, for the first time, isolated from muscle tissue extracts and, due to that, its name derived from *carnis*, the Latin word for meat [5]. Around 20 years later, in 1927, its chemical structure was identified (3-hydroxy-4-*N,N,N*-trimethylaminobutyric acid) [6]. Carnitine is a water soluble quaternary amine [6] and exists in two isoforms, but only the L-isomer is biologically

active [7,8]. L-carnitine is a compound that occurs naturally within the body and exists in all mammalian species [9]. In humans, more than 95% of the body's total carnitine stores exists within skeletal muscle tissue [10], not only as free L-carnitine, the principal component of the skeletal muscle carnitine pool, but also as short-, medium-, and long-chain esters that are often called acyl-carnitines [9].

L-carnitine is well-known for its two important roles in human metabolism, namely in skeletal muscle. In the mitochondria, L-carnitine is located in the intermembrane space [11] and its main function and the most documented one is to assist in the translocation of long-chain fatty acids (acyl groups) into the mitochondria matrix, for subsequent β -oxidation [12]. The other metabolic role is the regulation of mitochondrial acetyl-coenzyme A (acetyl-CoA)/free coenzyme A (CoASH) ratio [12].

Based on its metabolic roles, L-carnitine dietary supplements gained a lot of popularity latter in the 20th century [13]. The main premises were that if dietary L-carnitine supplementation increased L-carnitine's availability within human body, it would result in increased lipid oxidation, spared muscle glycogen stores and, thus delay the onset of fatigue and perhaps improve exercise performance and fat loss [12,14]. Therefore, research has been directed towards that [12]. However, achieving the desired ergogenic effects

in healthy humans, early from the beginning, has revealed to be more difficult than what the theoretical basis indicated [15–18]. Three previous reviews [16–18] described early L-carnitine supplementations studies, as well as, possible limitations in the study designs. So, as a consequence of the inconsistent results, research regarding this topic slowed down.

More recently, although not as much as previously, new and important research with L-carnitine supplementation and exercise, in healthy humans, has been done, renewing the interest in this supplement. With this in mind, we thought it was time to review the available data, mainly the most recent, to understand if L-carnitine can, indeed, be considered an ergogenic supplement, as well as to know its potential uses. Moreover, will also be briefly analyzed the L-carnitine supplementation effects in weight-loss, recovery after exercise and aging.

2. Methodology

A literature search was conducted to identify studies related to L-carnitine supplementation and athletic performance. PubMed and Scopus were the online scientific database used from March to August 2018. A combination of the following keywords was used as search terms: “athletes”, “L-carnitine”, “sports”, “supplementation” and “performance”. References of retrieved articles were used whenever they were considered relevant. Additionally, the book *Harpers Illustrated Biochemistry* [11] was used to search the role of L-carnitine in fatty acid metabolism. Based on the titles and abstracts, the relevance of the publications was judged. Studies whose outcome was not related to exercise performance were included whenever studies in athletes were not available, or if necessary to describe important research. Were only considered human trials.

3. L-carnitine absorption and biosynthesis

Healthy humans maintain L-carnitine balance by biosynthesis within the body (in liver, kidneys, and brain [19]), absorption from dietary sources (humans can obtain around 75% of L-carnitine from dietary intake [8], mainly through the ingestion of animal-based food products [20,21]), and through elimination and reabsorption by kidneys [22]. L-Carnitine can be biosynthesized from two essential amino acids, lysine and methionine, and requires vitamin C, vitamin B1, vitamin B6 and ferrous iron as cofactors [22,23]. Cardiac and skeletal muscle, due to the impossibility of synthesizing L-carnitine, have to acquire it from plasma [8]. The quantities that can be obtained from dietary intake are very variable and depend upon individual’s food choices [21,22]. Meats, mainly red meats, and dairy products are the main sources, however, L-carnitine can also be found in fruits and vegetables, but the amounts are negligible [9]. Vegans are the ones who typically acquire less, usually less than 1 μmol carnitine/kg body weight/day. Individuals who consume dairy products, chicken and fish, but little or no red meat, can acquire ~ 1 to 8 μmol carnitine/kg body weight/day. The highest amounts are obtained by those who regularly consume red meat and can vary from 6 to 15 μmol carnitine/kg body weight/day [22]. Vegetarians have smaller stores com-

pared to omnivores [24], however besides also being able to biosynthesize endogenously, seems to exist a compensatory mechanism for the reduced ingestion with a higher bioavailability of L-carnitine from food [25]. Thus, L-carnitine is considered a conditionally essential nutrient, since in some conditions, the individual requirements might be higher than the amounts one can obtain from the diet and biosynthesis [8]. L-carnitine has a very low bioavailability and absorption, a very high renal clearance and its transport into tissues is made by an active transport [8]. Bioavailability of oral L-carnitine dietary supplements is around 14 to 18%, with the unabsorbed portion being degraded in the large intestine [22].

4. L-carnitine metabolism during exercise

L-carnitine has two main roles within skeletal muscle that are illustrated in Fig. 1 and described below.

On one hand, in skeletal muscle, L-carnitine, as a substrate for carnitine palmitoyltransferase 1 (CPT1), has an essential role in the translocation of long-chain fatty acids (acyl groups) into the mitochondrial matrix, for subsequent β -oxidation [11,26,27]. CPT1, located on the outer mitochondrial membrane, is the protein responsible for this process [11].

On the other, during high-intensity exercise, large quantities of acetyl-CoA are produced via fast glycolysis. These acetyl-CoA molecules enter the mitochondrial matrix and supersede the utilization of the tricarboxylic acid (TCA) cycle [12,28]. Therefore, L-carnitine’s second role is to regulate the ratio of CoASH to acetyl-CoA. In this reaction, catalyzed by carnitine acetyltransferase (CAT), free L-carnitine accepts an acetyl-CoA molecule and forms acetyl-L-carnitine. This reaction also results in an increase in CoASH that can posteriorly be utilized in ATP generation, for example, through TCA cycle [12]. Thus, free L-carnitine buffers the excess acetyl-CoA production when its rate of formation from pyruvate oxidation are higher than the TCA cycle demand, which is what happens during high-intensity exercise [12,28]. Consequently, skeletal muscle carnitine content falls as acylcarnitines accumulate, monopolizing the available free L-carnitine [29,30]. Acetyl-L-carnitine is the dominant acylcarnitine [16]. Therefore, using free L-carnitine to form acetyl-L-carnitine depletes skeletal muscle free carnitine pool, which reduces the availability of free L-carnitine in the reaction catalyzed by CPT1 [31]. CPT1 concentrations are regulated by exercise intensity. While its concentrations are increased at 60% maximal oxygen consumption ($\text{VO}_{2\text{max}}$), when intensity rises above 75% $\text{VO}_{2\text{max}}$, muscle free carnitine decreases progressively due to the formation of CPT1 and buffering of excess acetyl-CoA [12,28]. This decrease is the reason why this protein is considered the rate-limitation step in lipid oxidation, namely during exercise [32,33].

In an opposite direction, if a second bound of exercise is performed [34], or if exercise is continued for several hours [35], the acetyl-CoA availability may be lower than the demands of the TCA cycle. When this happens, the accumulation of acetyl-L-carnitine provides a store of acetyl groups, which via the reverse CAT reaction, become ready to be used by the TCA cycle [12,32].

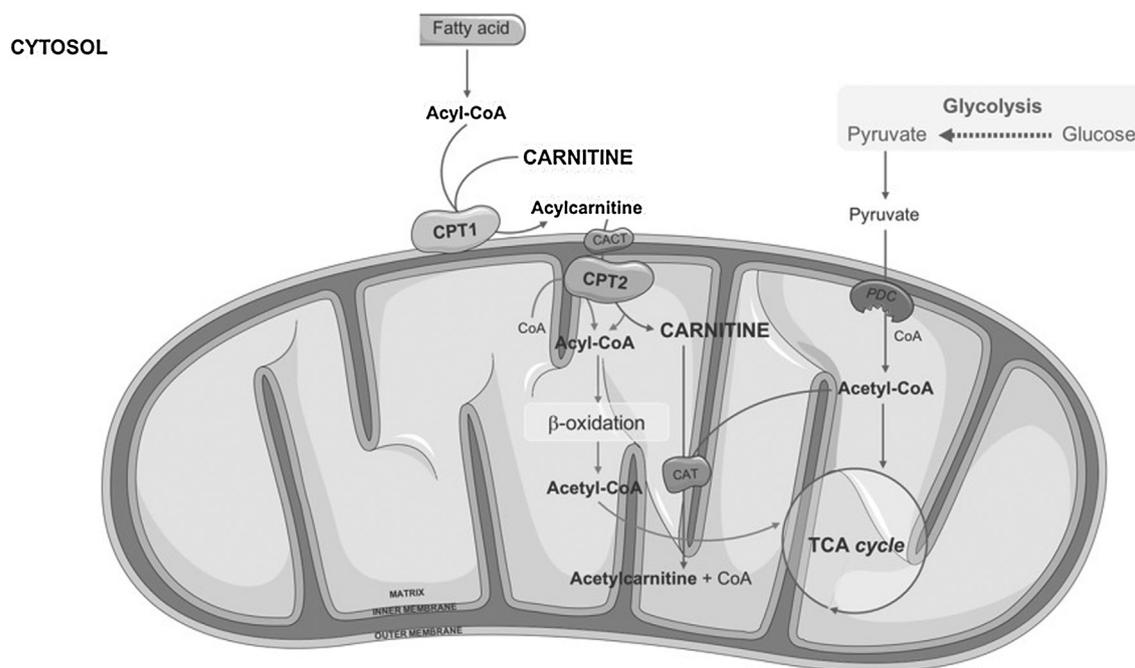


Fig. 1 Roles of L-carnitine within skeletal muscle. L-carnitine shuttles long-chain fatty acids inside the mitochondria by forming acylcarnitine. This molecule is then transported in to the mitochondrial matrix by carnitine acetyltransferase 1 (CPT 1) and carnitine acetyltransferase 2 (CPT 2). Fatty acids are then broken down in β -oxidation, which results in the formation of acetyl-CoA that can posteriorly be utilized in tricarboxylic acid (TCA) cycle, generate ATP. L-Carnitine second role is to modulate the ratio of free coenzyme A to acetyl-CoA. Free L-carnitine combines with excess acetyl-CoA that accumulate during high-intensity exercise, forming acetyl-L-carnitine and coenzyme A. CAT: carnitine acetyltransferase; CoA: coenzyme; CPT: carnitine palmitoyltransferase; PDC: pyruvate dehydrogenase complex; TCA: tricarboxylic acid.

A thorough review of the L-carnitine role in fatty-acid transport and in skeletal muscle fuel metabolism is provided by Stephens and collaborators [12].

5. L-carnitine retention on skeletal muscle

Studies that will be presented next do not involve athletes nor was performed any exercise, however, their results are relevant to explain an important step taken in L-carnitine supplementation study, mainly in muscle L-carnitine retention.

Early studies, either orally or with intravenous L-carnitine administration per se, failed to increase skeletal muscle carnitine content [16,17,36,37]. Besides, a recent study that compared L-carnitine supplementation of vegetarians and omnivorous, reported that only the vegetarian group, who started with fewer reserves, increased their muscle carnitine content [24]. The difficulty in increasing skeletal muscle carnitine content is, in part, caused by the high carnitine concentration gradient between muscle (~ 3.5 mmol/L) and plasma ($50 \mu\text{mol/L}$) [7,38,39]. L-carnitine is transported across the sarcolemma through the organic cation transporter 2 (OCTN2) [39,40]. The K_m for this protein, in vitro, is $4.3 \mu\text{mol/L}$ [40], which suggest that in basal state, skeletal muscle carnitine uptake is saturated. Therefore, simply increasing L-carnitine ingestion per se is unlikely to result in skeletal muscle carnitine accumulation [12]. OCTN2 is stimulated by extracellular Na^+ and, thus through increasing the activity of the Na^+/K^+

pump, transport can be increased [12]. Knowing that insulin increases sarcolemmal Na^+/K^+ ATPase pump activity [40,41] and, thus intracellular Na^+ flux, on an attempt to promote skeletal muscle carnitine retention, a research group [36] took science one step forward and tested an alternative strategy.

Stephens et al. [36] hypothesized that insulin would augment Na^{\pm} dependent skeletal muscle carnitine transport via OCTN2 and, consequently, increase muscle carnitine content. This study consisted in a 5 h intravenous L-carnitine infusion ($\sim 500 \mu\text{mol/L}$), as well as an insulin infusion maintaining serum levels at physiologically high concentrations (~ 150 mU/L). Results were in accordance with what was expected and a 13% increase in muscle total carnitine content as well as an increase in OCTN2 mRNA expression were reported. An intravenous infusion of high concentration of plasma carnitine per se (insulin maintained at fasting) was also tested and the lack of results confirmed what was thought previously.

A second study [31], from the same group, replicated the protocol and reported an increase of 15% on muscle total carnitine content. Associated with this augment was a 30% decrease in pyruvate dehydrogenase enzyme complex activation (PDCa), a 40% decrease in muscle lactate and, also, a 30% increase in muscle glycogen and a 40% increase in long-chain acyl-CoA content. The authors suggested that an increase in skeletal muscle total carnitine results in a reduction in carbohydrate utilization under high carbohydrate availability, which was possibly caused by an increase in lipid oxidation, mediated by L-carnitine.

Table 1 Summary of studies analyzing the effect of dietary L-carnitine with carbohydrates supplementation (no exercise performed).

References	Subjects	Age (mean)	Dose of L-carnitine/Duration	Outcome
				Muscle content
[39]	22 healthy, untrained, non-vegetarian men (8 in study A and 14 in study B, 7 for each group—control and carnitine)	Study A: 21.9 ± 0.6 yrs	3 g/d + 4 × 94 g CHO (1, 2.5, 4 and 5.5 h after L-carnitine) in 2 visits, 2 wks apart	Whole body carnitine retention (indirect measurements)
		Study B: Control: 20.4 ± 0.2 yrs Carnitine: 20.9 ± 0.3 yrs	3 g/d + 2 × 94 g CHO (1 and 4 h after L-carnitine), for 2 wks	
[55]	7 healthy, non-vegetarian men	24.2 ± 5.0 yrs	3 g L-carnitine	No net uptake across the forearm
			3 g L-carnitine + 80 g CHO (1 h after L-carnitine)	↑ 0.25%/d across forearm
			3 g L-carnitine + 40 g CHO + 40 g whey protein (1 h after L-carnitine)	No net uptake across the forearm

CHO: carbohydrates; d: day; g: grams; h: hours; wks: weeks; yrs: years.

Together, these two studies demonstrated that muscle total carnitine content can be increased if hypercarnitinemia is combined with hyperinsulinemia. After, the same group investigated the serum insulin concentration needed to produce the desired effects and concluded that it is only possible with concentrations ≥ 90 mU/L [42]. Hereupon, increases in skeletal muscle L-carnitine retention were reported, however the mechanism by which it was achieved was impractical. So, besides its importance, this work was still far from showing an ergogenic effect. Therefore, the next step was to investigate whether an oral co-ingestion of L-carnitine supplementation, with an amount of dietary carbohydrates capable of stimulating serum insulin concentrations to required levels, would augment muscle carnitine content [39].

The following study, which tested this hypothesis, was published by Stephens et al. [39]. The investigation was divided into two separate studies, whose supplemental protocol is described on Table 1. Muscle biopsies were not performed but based on a decrease in L-carnitine urinary excretion, authors assumed that L-carnitine supplementation resulted in whole body L-carnitine retention. Moreover, considering dietary L-carnitine has a poor bioavailability (less than 15% for this dose), the authors predicted that if the supplementation was maintained for 100 days, would be possible to increase muscle carnitine content by 10%.

At that point in L-carnitine supplementation study, three studies [31,36,39] reported increases in skeletal muscle total carnitine content; however conditions in which these results were achieved, are not nearly ideal. In the first two [31,36], it was achieved through intravenous infusions of L-carnitine and insulin and, in the one who used carbohydrates to stimulate the same insulin effect, muscle biopsies were

not performed and its conclusion was based on an assumption [39]. Moreover, samples size were small, untrained individuals were recruited and, considering that the reason why L-carnitine supplementation has been studied is due to possible improvements in exercise performance, these results are not enough. Therefore, although being an important step considering past data, results in skeletal muscle using a co-ingestion of L-carnitine and carbohydrates, performed in athletes, are still needed.

6. L-carnitine supplementation and exercise

In this chapter, studies evaluating L-carnitine supplementation on exercise performance will be included and grouped by the type of exercise performed. Tables 1 and 2 provide more details and summarizes the results of studies that investigated a supplementation protocol of L-carnitine plus carbohydrates.

6.1. Cycling (various exercise intensities)

One study [43] performed in five rugby players, with the purpose of examining whether caffeine, carnitine or a mixture of both, could affect exercise endurance time via carnitine metabolism, reported not only that L-carnitine ingestion could promote fat oxidation resulting in higher endurance performance in athletes, but also that effects could be higher if carnitine was co-ingested with caffeine. However, the small sample size is a limitation.

The following three studies, from the same research group, did not add carbohydrates to L-carnitine supplementation. The first one, by Broad et al. [44], whose exercise

Table 2 Summary of studies analyzing the effect of dietary L-carnitine with carbohydrates supplementation.

Ref.	Subjects	Age (mean)	Dose of L-carnitine/Duration	Exercise tests	Outcome	
					Muscle content/Body composition	Exercise
[47]	14 healthy, non-smoking, non-vegetarian, recreational male athletes	25.9 ± 2.1 yrs	2 x (1.36g + 80 g CHO), at breakfast and 4 h later, for 24 wks.	30 min cycling at 50% VO _{2max} , 30 min at 80% VO _{2max} , 30 min work output performance trial	21% ↑ muscle total carnitine content	50% VO _{2max} : 55% ↓ glycogen utilization; 31% ↓ PDCa 80% VO _{2max} : better matching of metabolic flux Performance trial: 11% ↑ work output 6% ↑ energy expenditure ↔ Skeletal muscle maximal CPT1 activity
[49]	12 healthy, non-vegetarian, male recreational athletes (6 for each group—control and carnitine)	Control: 25.3 ± 2.1 yrs Carnitine: 28.5 ± 2.1 yrs	2 x (1.36 g + 80 g CHO), at breakfast and 4 h later, for 12 wks.	30 min on the cycle ergometer at a workload corresponding to 50% VO _{2max}	21% ↑ muscle total carnitine content ↑ Total body mass in Control but no in Carnitine ↔ Lean body mass	↔ Skeletal muscle maximal CPT1 activity
[51]	21 healthy, non-vegetarian, untrained males	23 ± 2 yrs	2 x (1.5 g + 80 g CHO), for 24 wks in combination with HIIT training. Ingestions occurred first thing in the morning and 4 h later	2 × 3 min bouts of cycling at 100% Watt _{max} , with 5 min of rest (14 repeated the protocol following 24 wks of HIIT)	30% ↑ muscle free carnitine at rest	9% ↑ VO _{2max} ; 15% ↑ Watt _{max} ; 23% ↑ work output during training in Control and Carnitine; ↔ Between groups. No differences other than those obtained from HIIT alone
[52]	10 moderately active males	27 ± 4.83 yrs	1st bottle (3 g L-carnitine), 3 h prior to exercise; 2nd bottle (94 g CHO) 2 h prior to exercise; 3rd bottle (94 g CHO) 30 min prior to exercise	3 testing sessions; 40 min of cycling at 65% VO _{2peak} , followed by cycling to exhaustion at 85% VO _{2peak}	↔ skeletal muscle carnitine content.	↓ RER at baseline; ↓ Blood lactate after 10 min of cycling at 65% VO _{2peak} ; ↔ Power output; ↔ Time to exhaustion

CHO: carbohydrates; CPT1: carnitine palmitoyltransferase 1; g: grams; h: hours; HIIT: high-intensity interval training; PDCa: pyruvate dehydrogenase enzyme complex activation; RER: respiratory exchange ratio; VO_{2max}: maximal oxygen consumption; VO_{2peak}: peak oxygen uptake; Watt_{max}: maximal workload; wks: weeks; yrs: years.

trials consisted of 90 minutes of steady-state cycling with a subsequent 20 km time trial, found no effects on substrate utilization with a supplementation of 2 g of L-carnitine during four weeks in a group of trained subjects. A later

study [45], tested the same L-carnitine dose but during half of the time. Active subjects exercised for 90 minutes at 70% VO_{2max} after two days of consuming a prescribed diet before and after supplementation. Final results indicated

that fat, carbohydrate, and protein contribution to metabolism during cycling exercise was not affected by this protocol [45]. A posterior one [46], still from the same group, this time with athletes, evaluated the effects of 2 g of L-carnitine supplementation for 15 days on metabolic responses to graded-intensity exercise [20 minutes bouts of exercise over a range of intensities (20–80% peak oxygen uptake (VO_{2peak}))] under conditions of altered substrate availability. The authors reported that L-carnitine may induce subtle alterations in substrate handling in metabolically active tissue when fatty acid availability is increased. However, no effects were observed in whole-body substrate utilization during short-duration exercise at the intensities studies [46].

In 2011, a study by Wall et al. [47] with recreational athletes, showed, for the first time, that muscle carnitine content can be increased in healthy men by dietary carnitine supplementation. It involved 24 weeks of twice-daily ingestion of 1.36 g of L-carnitine in combination with 80 g of carbohydrates. Results showed a 21% increase on muscle total carnitine. Besides, this study also demonstrated that the influence of L-carnitine supplementation on exercise metabolism depends on exercise intensity, since a 55% reduction in muscle glycogen utilization was found during cycling at 50% VO_{2max} but not at 80% VO_{2max} . According to the authors, this spare of muscle glycogen possibly suggests an increase in lipid oxidation during exercise (altering muscle metabolism) caused by a dietary-mediated increase in muscle total carnitine stores, which supports the suggestion that free L-carnitine availability is limiting to the CPT1 reaction. At 80% VO_{2max} muscle lactate content was 44% lower and a better maintenance of the ratio phosphocreatine to ATP was observed. Relatively to PDCa status, it was reduced at 50% VO_{2max} but increased at 80% VO_{2max} . A comment on this study [48] referred that not measuring lipid oxidation was a limitation, since it should have been one of the primary outcomes.

Two year later, a subsequent study [49], investigated if twice-daily ingestion of 1.36 g of L-carnitine plus 80 g of carbohydrates during 12 weeks, could modulate energy metabolism. Similar to the previous, this study showed a 21% increase in muscle carnitine content at 50% VO_{2max} . The authors referred that this augment contributed to the maintenance of the capacity to oxidize fat, which prevented an increase in body fat mass in carnitine group. Unlike this result, in the control group was observed an increase in adiposity attributed to excess energy intake from carbohydrate beverage. Moreover, in the L-carnitine group, a 6% increase in energy expenditure was observed for which authors referred it was most likely due to the greater change in the rate of fat oxidation that happened in the L-carnitine group, in the absence of a change in the rate of carbohydrate oxidation [49].

However, in a review of L-carnitine and fat oxidation, Stephens et al. [50], referred that the long-held belief that carnitine supplementation could improve endurance performance via augmenting its role in fat oxidation should be revised, and that more emphasis should be given to the major role L-carnitine plays in carbohydrate metabolism during exercise. Therefore, in a very recent study, Shannon et al. [51] investigated whether increasing skeletal muscle L-carnitine, and thereby its buffering capacity, could alter

the metabolic and physiological adaptations to 24 weeks of high-intensity interval training (HIIT) at 100% maximal workload ($Watt_{max}$). Results showed that L-carnitine supplementation, despite the increases in muscle free carnitine content, did not bring any benefits other than the ones obtained from HIIT alone. Results from this study seem to show that increasing skeletal muscle carnitine content may not be enough to achieve results in performance, other than in low-intensity exercise. For that reason, other supplementation protocols more targeted to the second role of L-carnitine should be investigated.

In another study, also published this year, Burrus et al. [52] evaluated a single ingestion of 3 g L-carnitine and two subsequent drinks with 94 g of carbohydrate each in a sample of moderately active subjects. Authors concluded that, despite differences in some parameters, ingestion of L-carnitine and carbohydrates in an acute approach does not seem to influence exercise metabolism due to insufficient changes in skeletal muscle L-carnitine content. However, since muscle biopsies were not performed, this supposition cannot be confirmed. Notwithstanding, considering that the amount of carbohydrates and L-carnitine used previously showed positive results [47,49], although the absence of muscle biopsies, this study may be important to show that possibly only chronic protocols work with L-carnitine, due to its low bioavailability.

In the present chapter, were observed mixed results in the L-carnitine supplementation effects on exercise performance. In the three studies [44–46], in which was evaluated an ingestion of L-carnitine *per se*, no positive results were found or, if so, it was very little pronounced. In opposition, in the studies presented next [47,49,51,52], which evaluated a co-ingestion of carbohydrates and L-carnitine, only the ones with long-term strategies found promising results.

6.2. Running (treadmill)

A study [53], performed in soccer players, evaluated the effect of acute L-carnitine loading on endurance performance. For the exercise test, athletes began running at 8 km/h and then continued at 10 km/h. The speed was increased 1 km/h every 3 minutes until subjects chose to quit. Regarding the results of this study, the authors reported that a single supplementation of 3 or 4 g of L-carnitine taken before physical exercise affected performance positively in terms of running speed corresponding to specific lactate concentrations and also reduced heart rate. Moreover, authors suggested that this amount of L-carnitine taken before exercise prolonged exhaustion. However, seems that final conclusions were imprudent considering the methodologies used.

Another study [54], aimed to investigate the acute effects of L-carnitine supplementation on aerobic efficiency and compared sedentary with athletic men. The exercise program was performed using a treadmill. After the warm up (3 minutes at 2.3 km/h on a 0% slope), the speed and degrees of slope were changed every 3 minutes according to the Bruce protocol. Subjects had to run continuously until 80% of their theoretical maximal heart rate. Regarding the results of this study, despite some

limitations mentioned by authors, they concluded that an acute L-carnitine supplementation possibly affects exercise performance in athletes but not in sedentary men. Hereupon, although no conclusion on L-carnitine supplementation in athletes can be made from this study, it may be useful to reinforce the idea that studies need to be performed in athletes. Therefore, and at this time, little information exists that supports the recommendation of L-carnitine use. More research is needed, and it is crucial to include athletes.

7. Alternative strategy to stimulate insulin effect

As previously showed [39,47,49,51], a high carbohydrate ingestion is able to stimulate insulin and, therefore, increase skeletal muscle carnitine content. However, the amounts of carbohydrates required can be impractical and when ingested per se could alter body composition, as showed in a control group [49]. So, the next step was to investigate other ways to reduce the carbohydrate load. Shannon et al. [55], investigated whether reducing carbohydrates by associating it with whey protein, could achieve the same effects. Results showed that in the group who ingested carbohydrates and protein, despite similar elevation in serum insulin and similar plasma flow response induced, the supplementation protocol prohibited any increase in net carnitine balance (NCB). Therefore, authors suggested that the insulin-mediated increase in forearm carnitine balance observed with carbohydrate consumption was acutely blunted by a carbohydrate plus protein beverage, which might indicate that the mechanism by which insulin stimulates carnitine transport into skeletal muscle is antagonized by a large bolus of whey protein. As such, an alternative strategy is still needed.

8. L-carnitine supplementation and weight loss

The theoretical basis for L-carnitine supplementation as a weight-loss agent is based on the assumption that increasing L-carnitine ingestion, through supplementation, would increase fat oxidation, leading to the progressive reduction of body fat reserves [18]. However, as previously referred, to achieve increases in skeletal muscle carnitine content, a high dose of carbohydrates needs to be ingested.

Although not performed in athletes but mainly in obese and diabetic women, for the comprehensive purpose of this review it is worth to consider a recent study published on this topic. In 2016, a systematic review and meta-analysis by Pooyandjoo et al. concerning the effect of L-carnitine on weight loss in adults was published [56]. Authors concluded that carnitine might be effective for weight loss in adults; however, considering the existing difficulty to increase skeletal muscle carnitine content without ingesting a considerable high amount of carbohydrates, this statement was seen as surprising and a bit risky. As expected, some methodological and practical issues can be found. Possible incorrect aspects were commented latter [57].

9. L-carnitine supplementation on recovery after exercise and aging

Results in the L-carnitine supplementation and exercise performance studies have always been inconsistent. Therefore, the focus of clinical research shifted toward evaluating the impact that this dietary supplement could have on recovery after exercise [14,20]. According to results of recent reviews on L-carnitine supplementation and recovery [14,20], seems that L-carnitine could reduce tissue damage and muscle soreness and improve recovery after exercise. Moreover, and based on current animal studies, a preventive role of L-carnitine in age-associated muscle protein degradation and a regulation of mitochondrial homeostasis is suggested [20]. Additionally, a study in healthy older adults, evaluated the impact that a multi-ingredient supplement with L-carnitine, creatine, and L-leucine could have on this population. The authors found that it significantly enhanced lean muscle mass and functional strength particularly in the lower legs. According to the authors, it was likely due to an improved protein anabolism through the mammalian target of rapamycin (mTOR) pathway. Moreover, authors also pointed that the addition of L-leucine and creatine may have synergistic actions in muscle protein synthesis when incorporated with L-carnitine [20,58]. Therefore, other potential uses of L-carnitine supplementation should be studied, for example in this area.

10. Critical opinion, unresolved questions and opportunities for future research

Almost all of the published studies concerning L-carnitine supplementation and its ability to increase skeletal muscle carnitine content have come from the same laboratory. Besides, when results in exercise performance with L-carnitine supplementation were achieved, exercise was performed at 50% $\text{VO}_{2\text{max}}$, however, in most cases, athletes do not compete at low intensity levels. Moreover, if the goal is to establish a relation between a dietary supplement and its ability to improve performance, research has to be performed in athletes. However, that is not the case in the majority of published work. Hence, research is still needed.

Another fact that cannot be forgotten is that most studies used very small samples and, taking into account that there is individual variability, it is not known whether the results would be replicated in others.

In addition, further research on other alternative ways to stimulate serum insulin concentrations orally that could reduce the carbohydrate load is necessary. Moreover, it seems that L-carnitine supplementation might be helpful in older people, so research on this topic should continue.

Finally, other opportunities for future research include the study of L-carnitine supplementation in specific populations, such as diabetic patients. In an interesting study of Reynier et al. [59], the impact of L-carnitine associated with lysine and methionine supplementation was evaluated in different situations, with and without exercise. Positive results regarding a decrease in the feeling of muscular weakness and myalgia and an increase in exercise aerobic performance, insulin sensitivity, basal insulin efficiency

and in the overall glucose tolerance were only found in the groups of subjects with impaired glucose tolerance or with non-insulin dependent diabetes mellitus. These results were attributed, in part, to the improvement in insulin sensitivity and, in general, to the L-carnitine buffering effect, which prevents the excess acyl-CoA accumulation. Besides, a review on this topic by Ringseis and collaborators [60] pointed that L-carnitine supplementation might be an effective tool for improvement of glucose utilization in obese type 2 diabetic patients. Therefore, more research should be done and, whenever possible, exercise testing should be included. Additionally, it would be interesting to investigate the impact of L-carnitine supplementation in the diabetic athlete.

11. Conclusion

In conclusion, it was showed that increasing skeletal muscle carnitine content, in some specific situations, could influence fuel selection during exercise and, perhaps, increase fat utilization. However, it is likely that during high-intensity exercise, due to its buffering role, free L-carnitine is limiting the CPT1 reaction. Therefore, the problem still resides in the ability to increase muscle carnitine content. Although no longer being a major concern, since it was showed that a L-carnitine supplementation with carbohydrates can increase skeletal muscle carnitine, it remains difficult to achieve. No doubt that an oral co-ingestion of carbohydrates and L-carnitine is more practical than the intravenous infusion of L-carnitine and insulin, and more importantly, legal. However, the amounts of carbohydrates required to achieve the ergogenic effects make it still impractical on a daily basis in the majority of the situations and could decrease adherence. Besides that, high carbohydrate loads are incompatible, in most cases, with weight loss diets. Plus, it only seemed achievable in chronic protocols (≥ 12 weeks), which means that high quantities of carbohydrates need to be ingested during long periods of time.

Therefore, despite that some performance benefits have been demonstrated, the available data still is not enough to widely recommend L-carnitine supplementation with the aim of improving exercise performance.

Disclosure of interest

The authors declare that they have no competing interest.

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