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The Effects of L-Carnitine Supplementation in Athletic Performance

Efeitos da Suplementação com L-Carnitina no Rendimento Desportivo

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ABSTRACT

The use of dietary supplements is very common in the general population, but mainly among athletes, aiming to improve exercise performance. While some substances may have scientifically proven ergogenic effects, in most cases, claims are mere assumptions based on the roles substances have in human metabolism.

L-Carnitine dietary supplements have become very popular due to two crucial roles L-carnitine has in skeletal muscle metabolism. L-Carnitine's main function is to assist in the translocation of long-chain fatty acyl groups into the mitochondria, for subsequent β-oxidation. The second role is to buffer the excess acetyl-CoA, which contributes to the regulation of the ratio of free coenzyme A to acetyl-CoA in the mitochondrial matrix. Due to these important functions, since late in the 20th century, has been said that if L-carnitine dietary 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 which, in the end, would result in improvements in exercise performance.

This review aims to analyze available data, on the effects of L-carnitine in exercise performance and, therefore, to understand if its claims can be justified by scientific evidence. Moreover, this review will also focus on other L-carnitine claims such as, weight loss and recovery after exercise.

RESUMO EM PORTUGUÊS

O uso de suplementos alimentares é muito comum na população em geral, mas principalmente em atletas, com a finalidade de melhorar o seu rendimento desportivo. Enquanto algumas substâncias têm efeitos ergogénicos cientificamente comprovados, na maior parte dos casos, estas alegações são meras especulações baseadas nas funções das substâncias no metabolismo humano.

Os suplementos alimentares de L-carnitina têm-se tornado muito populares devido aos dois papéis cruciais que a L-carnitina tem no metabolismo muscular. A principal função da L-carnitina é assistir na translocação de ácidos gordos de cadeia longa para a mitocôndria, para subsequentemente serem oxidados. O outro papel é o tamponamento do excesso de acetil-CoA, contribuindo para a regulação do rácio coenzima A livre/acetil-CoA na matriz da mitocôndria. Devido a estas funções importantes, desde o final do século XX, tem vindo a ser referido que se a suplementação com L-carnitina aumentasse a disponibilidade de L-carnitina no corpo humano, resultaria num aumento da oxidação lipídica, na poupança das reservas de glicogénio muscular e, como tal, atrasaria a fadiga que, por último, resultaria em melhorias do rendimento desportivo.

Esta revisão tem como objetivo analisar a informação disponível relativamente aos efeitos da L-carnitina no rendimento desportivo e compreender se as suas alegações podem ser justificadas por evidência científica. Além destes, irá também abordar outras alegações da suplementação com L-carnitina, como por exemplo, a perda de peso e a recuperação após o exercício.

KEYWORDS

Dietary supplement, Exercise, Fat oxidation, Muscle Metabolism, Recovery

PALAVRAS-CHAVE EM PORTUGUÊS

Suplemento Alimentar, Exercício, Oxidação lipídica, Metabolismo Muscular, Recuperação

ABBREVIATION

CAT, carnitine acetyltransferase

CHO, carbohydrates

CoASH, free coenzyme A

CPT1, carnitine palmitoyltranferase 1

HIIT, high-intensity interval training

K_m, Michaelis-Menten constant

mRNA, messenger ribonucleic acid

PDC, pyruvate dehydrogenase enzyme complex

PDCa, pyruvate dehydrogenase enzyme complex activation

RER, respiratory exchange ratio

TCA, tricarboxylic acid

VO_{2max}, maximal oxygen consumption

$Watt_{max}$, maximal workload

SUMMARY

INTRODUCTION

The use of dietary supplements is very common not only among athletes but also in the general population.[1] However, while some substances may have scientifically proven claims, in most cases, these are assumptions based on the roles substances have in human metabolism.[2] Besides that, the information about a supplement efficacy can come from anecdotes/observations from athletes.[3]

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.[4] Around 20 years later, in 1927, its chemical structure was identified (3-hydroxy-4-*N,N,N*-trimethylaminobutyric acid).[5] Carnitine is a water soluble quaternary amine[5] and exists in two isoforms, but only the L-isomer is biologically active.[6, 7] L-carnitine is a compound that occurs naturally within the body and exists in all mammalian species.[8] In humans, more than 95% of the body's total carnitine stores exists within skeletal muscle tissue,[9] 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.[8] Healthy humans maintain L-carnitine balance by biosynthesis within the body (in liver, kidneys, and brain[10]), absorption from dietary sources (humans can obtain around 75% of L-carnitine from dietary intake,[7] mainly through the ingestion of animal-based food products[11, 12]), and through elimination and reabsorption by kidneys.[13] 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.[13, 14] Cardiac and skeletal muscle, due to the impossibility of synthesizing L-carnitine, have to acquire it from plasma.[7]

The quantities that can be obtained from dietary intake are very variable and depend upon individual's food choices.[12, 13] 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.[8] 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.[13] Vegetarians have smaller stores compared to omnivores,[15] 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.[16] 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.[7] 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.[7] Bioavailability of oral L-carnitine dietary supplements is around 14 to 18%, with the unabsorbed portion being degraded in the large intestine.[13]

L-carnitine is well-known for its two important roles in human metabolism, namely in skeletal muscle. In this organ, L-carnitine is located in intermembrane space.[17] The 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.[18] The other metabolic role is the regulation of mitochondrial acetyl-CoA/CoASH ratio.[18]

Based on its metabolic roles, L-carnitine dietary supplements gained a lot of popularity latter in the 20th century.[19] 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.[18, 20] This review will examine whether the claims associated with L-carnitine dietary supplementation in exercise performance, weight loss and recovery are justified.

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 June 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*[17] 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. Animal trials and studies whose outcome was not related to exercise performance were included whenever human studies and studies in athletes were not available. Were only considered trials in healthy subjects.

L-Carnitine metabolism during exercise

In skeletal muscle, L-carnitine, as a substrate for carnitine palmitoyltranferase 1 (CPT1), has an essential role in the translocation of long-chain fatty acyl groups into the mitochondrial matrix, for subsequent β-oxidation.[17, 21, 22] CPT1, located on the outer mitochondrial membrane, is the protein responsible for this process.[17]

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 TCA cycle.[18, 23] Therefore, L-carnitine's second role is to regulate the ratio of free coenzyme A (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 that is moved out of the mitochondrial matrix. This reaction also results in an increase in free coenzyme A that can posteriorly be utilized in ATP generation, for example, through tricarboxylic acid (TCA) cycle. 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.[18, 24] Consequently, skeletal muscle carnitine content falls as acylcarnitines accumulate, monopolizing the available free L-carnitine.[24, 25] Acetyl-L-carnitine is the dominant acylcarnitine.[26]

In summary, 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.[27] CPT1 concentrations are regulated by exercise intensity. While its concentrations are increased at 60% VO_{2max}, when intensity rises above 75% VO_{2max}, muscle free carnitine decreases progressively due to the formation of CPT1 and buffering of excess acetyl-CoA.[18, 23] This decrease is the reason why this protein is considered the rate-limitation step in lipid oxidation, namely during exercise.[28, 29] A thorough review of the L-carnitine role in fatty-acid transport and in skeletal muscle fuel metabolism is provided by Stephens and collaborators.[18]

Due to these important roles, over the years, it has been hypothesized that if L-carnitine supplementation increased muscle L-carnitine content, athletic performance could be increase and thus research has been directed toward that.[18] 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.[2, 26, 30, 31] Three previous reviews[2, 26, 31] described early L-carnitine supplementations studies, as well as, possible limitation in study designs. For future reference, L-carnitine doses ingested varied from 2 to 6 g/day.

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.[26, 31-33] In line, a recent study that compared vegetarians with omnivorous, reported that only the vegetarian group, who started with fewer reserves, increased its muscle carnitine content.[15] These lack of results is, in part, caused by the high carnitine concentration gradient between muscle (~3.5 mmol/l) and plasma (50 μmol/l).[6, 34, 35] L-carnitine is transported across the sarcolemma through the organic cation transporter 2 (OCTN2).[35, 36] The K_m for this protein, *in vitro*, is 4.3 μmol/l,[36] which suggest that in basal state, skeletal muscle carnitine uptake is saturated. Therefore, simply increasing L-carnitine ingestion *per se* is unlike to result in skeletal muscle carnitine accumulation.[18] OCTN2 is stimulated by extracellular Na^+ and, thus through increasing the activity of the Na^+/K^+ pump, transport can be increased.[18] Knowing that insulin increases sarcolemmal Na^+/K^+ ATPase pump activity[36, 37] and, thus intracellular Na^+ flux, on an attempt to promote skeletal muscle carnitine retention, a research group took science one step forward and tested an alternative strategy.

Stephens *et al.*[32] hypothesized that insulin would augment Na^+-dependent skeletal muscle carnitine transport via OCTN2 and, consequently, increase muscle carnitine content. This study consisted in a 5 h intravenous L-carnitine infusion (~ 500 μmol/l), as well as an insulin infusion maintaining serum levels at physiologically high concentrations (~ 150 mU/l). The 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,[27] 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 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. 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.[38] 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.[35]

The following study, which tested this hypothesis, was published by Stephens *et. al.*.[35] 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 type of 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[27, 32, 35] reported increases in skeletal muscle total carnitine content, however conditions in which these results were achieved, are not nearly ideal. In the first two,[27, 32] 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.[35] Moreover, samples size was reduced, 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 results, results in skeletal muscle using a co-ingestion of L-carnitine and carbohydrates, performed in athletes, are still needed.

From now on, studies in athletes will be discussed or, if not available, studies with healthy people performing exercises will be included. Table 1 summarizes the results of studies that investigated a supplementation of L-carnitine plus carbohydrates.

L-Carnitine supplementation and exercise (varied range of intensities)

- **Athletes / recreational athletes / active or moderately active**

The following three studies did not add carbohydrates to L-carnitine supplementation. The first one, by Broad et al.[39], whose exercise trials consisted of 90 min 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. A later study, from the same group, tested the same L-carnitine dose but during half of the time. Participants 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.[40] The last one, also from the same group, studied the effects of 2 g of L-carnitine supplementation for 15 days on metabolic responses to graded-intensity exercise under conditions of altered substrate availability. The author 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.[41]

In 2011, a study by Wall *et. al.*[42] showed, for the first time, that muscle carnitine 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 was observed a better maintenance of the ratio phosphocreatine to ATP. Relatively to PDCa status, it was reduced at 50% VO_{2max} but increased at 80% VO_{2max}. A comment on this study(43) 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, 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 control group was observed an increase in adiposity attributed to excess energy intake from carbohydrate beverage. Moreover, in carnitine group, was observed a 6% increase in energy expenditure for which authors referred it is 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.(44)

In a very recent study, Burrus *et. al.*(45) tested the ingestion of 3 g L-carnitine and two subsequent drinks with 94 g of carbohydrate. 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[42, 44], although the absence of muscle biopsied, this study may be an important one to show that possibly only chronic protocols work with L-carnitine, due to its low bioavailability.

One study performed in five rugby players, which purpose was to examine whether caffeine, carnitine or a mixture of both, could affect exercise endurance time via carnitine metabolism, reported that L-carnitine ingestion could promote fat oxidation and endurance performance in athletes, and also that effects could be higher if carnitine was co-ingested with caffeine.[46] Another study, performed in soccer players, 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.[47]

In the present chapter, mixed results were observed. The first three, which did not include carbohydrates in supplementation protocols, found no result or if so, they were very little pronounced. In opposition, studies presented next, which tested a co-ingestion of carbohydrates and L-carnitine, only the ones with long-term strategies found promising results. Regarding the last two, while the first one had a really small sample, in the second one, seems that final conclusions were imprudent considering the methodologies used. Therefore, more research is needed and it is crucial to include athletic population.

- **Healthy, untrained**

In a review of L-carnitine and fat oxidation, Stephens *et al.*[48], 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.*[49] investigated whether increasing skeletal muscle L-carnitine, and thereby its buffering capacity, could alter the metabolic and physiological adaptations to 24 weeks of HIIT at 100% $Watt_{max}$. 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. More details about L-carnitine supplementation doses and results about can be found in Table 1. Results from this study could show that increasing skeletal muscle carnitine content may not be enough to achieve results in performance, other than in low-intensity exercise. Therefore, other supplementation protocols more targeted to the second role of L-carnitine should be investigated.

Results from the next two studies are interesting and worth mentioning. An animal study, comparing trained with untrained rats, besides an increases in fatty oxidation in skeletal muscle with L-carnitine supplementation, found that the effect of supplementation was even greater in trained rats that had received 3 weeks supplementation of carnitine.[50] Moreover, despite some limitations referred by the authors, a study performed in humans, compared sedentary subjects with athletes and concluded that an acute L-carnitine supplementation possibly affects exercise performance and triglycerides in athletes rather than in sedentary men.[51]

Hereupon, although no conclusion on L-carnitine supplementation in athletes can be made from these results two studies, they may be useful to reinforce the idea that studies need to be performed in athletic populations.

Alternative strategy to stimulate insulin effect

As previously showed,[35, 42, 44, 49] 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 control groups.[44] So, the next step was to investigate other ways to reduce the carbohydrate load. Shannon et al.[52], investigated whether reducing carbohydrates by associating it to whey protein, could achieve the same effects. Results showed that the group who ingested carbohydrates and protein, despite similar serum insulin achieved and plasma flow response induced, prohibited any increase in 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.

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.[2] However, as previously referred, to achieve increases in skeletal muscle carnitine content, a high dose of carbohydrates have to be ingested.

Although not performed in athletic population but mainly in obese and diabetic women, for the comprehensive purpose of this review it is worth to consider a recent study published in 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.[53] In an assertive way, authors concluded that "carnitine might be an effective drug for weight loss in adults". Considering the existing difficulty to increase skeletal muscle carnitine content, 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.[54]

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.[11, 20] According to results of recent reviews on L-carnitine supplementation and recovery, seems that L-carnitine could reduce tissue damage and muscle soreness[20] and improve recovery after exercise.[11, 20] Moreover, Fielding *et. al.*[11], referred that, based in current animal studies, a preventive role of L-carnitine in age-associated muscle protein degradation and a regulation of mitochondrial homeostasis is suggested. One example is a study in Labrador retrievers,[55] which reported that L-carnitine supplementation had beneficial effects on lean mass, activity intensity and also that it prevented exercise-induced muscle damage based on the reduced efflux of inflammatory enzymes and reduced oxidative stress during strenuous exercise. Regarding humans, a study that included L-carnitine in a multi-ingredient supplement found promising results in healthy older adults.[11, 56] Therefore, other potentials of L-carnitine supplementation should be studied, specially in this area.

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% VO_{2max}, however 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 athletic populations. However, that is not the case in the majority of published word. 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 clear that the results can 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. Finally, seems that L-carnitine supplementation might be helpful in older people so research in this topic should be made.

CONCLUSION

In conclusion, it seems 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 concerned, 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, however, the amounts of carbohydrates required to achieve the ergogenic effects makes it still impractical on a daily basis 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, which means that high quantities of carbohydrates need to be ingested during long periods of time.

Therefore, despite some ergogenic effects have been demonstrated, the available data still Is not enough to recommend L-carnitine supplementation with the aim of improving exercise performance.

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ANNEXES

Table 1: Summary of studies analyzing the effect of dietary L-carnitine and carbohydrates supplementation

Reference	Title	Subjects	Age (mean)	Dose of L-carnitine / Duration	Exercise tests	Outcome
(35)	Carbohydrate ingestion augments L-carnitine retention in humans	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 yr	3 g/d + 4 x 94 g CHO (1, 2.5, 4 and 5.5 h after L-carnitine ingestion) in 2 visits, 2 wks apart	No exercise	Whole body carnitine retention suggested by differences in plasma total carnitine concentration (Study A) and 24h urinary total carnitine excretion (Both studies).
			Study B Control: 20.4 ± 0.2 yrs Carnitine: 20.9 ± 0.3 yrs	3 g/d + 2 x 94 g CHO (1 and 4 h after L-carnitine ingestion), for 2 wks		
(42)	Chronical oral ingestion of L-carnitine and carbohydrate increases muscle carnitine content and alters muscle fuel metabolism during exercise in humans	14 healthy, non-smoking, non-vegetarian, recreational male athletes	25.9 ± 2.1 yrs	2 x (1.36g + 80 g CHO), for 24 wks. Ingestion occurred at breakfast and 4 h later	30 min cycling at 50% VO_{2max}, 30 min at 80% VO_{2max}, then 30 min work output performance trial	21% increase in muscle total carnitine content; 55% reduction in muscle glycogen utilization and 31% less PDCa, at 50% VO_{2max}. 11% increase in work output in the performance trial. Better matching of metabolic flux during high-intensity cycling (30 min at 80% VO_{2max}).
(44)	Skeletal muscle carnitine loading increases energy expenditure, modulates fuel metabolism gene networks and prevents body fat accumulation in humans	12 healthy, non-vegetarian, male recreational athletes (6 participants 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), for 12 wks. Ingestions occurred at breakfast and 4 h later	30 min on the cycle ergometer at a workload corresponding to 50% VO_{2max}	Mean increase of 21% in muscle total carnitine content. Total body mass increased in every subject in Control but did not change in Carnitine. No changes in lean body mass. 6% increase in energy expenditure in every subject in Carnitine. No differences in skeletal muscle maximal CPT1 activity. Skeletal muscle total long-chain acyl-CoA content under resting fasted conditions increased from a similar baseline concentration by approximately fourfold after 12 weeks in Carnitine, such that it was also fourfold greater than Control at this corresponding time point.
(52)	Protein ingestion acutely inhibits insulin-stimulated muscle carnitine uptake in health young men	7 healthy, non-vegetarian men	24.2 ± 5.0 yrs	3 g L-carnitine	No exercise	No net uptake across forearm.
				3 g L-carnitine + 80 g CHO (1 h after L-carnitine ingestion)		Approximately 0.25 %/d increase across forearm.
				3 g L-carnitine + 40 g CHO + 40 g whey protein (1 h after L-carnitine ingestion)		No net uptake across forearm.
(49)	Increasing skeletal muscle carnitine availability does not alter the adaptations to high-intensity interval training	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 x 3 min bouts of cycling exercise at 100% $Watt_{max}$, separated by 5 min of rest. (14 repeated this protocol following 24 weeks of HIIT)	Increase in VO_{2max} by ~9%, $Watt_{max}$ by ~15%, and work output during training by ~23% in control group and carnitine group with no difference between groups. Muscle free carnitine was 30% greater in carnitine vs control group at rest. No differences were found other that those obtained from HIIT alone.
(45)	The effect of acute L-carnitine and carbohydrate intake on cycling performance	10 moderately active males	27 ± 4.83 yrs	1st bottle (3 g L-carnitine), 3h prior to exercise session; 2nd bottle (94 g CHO) 2h prior to exercise; 3rd bottle (94 g CHO) 30 min prior to exercise	3 testing sessions; 40 min of cycling at 65% of VO_{2peak}, followed by cycling to exhaustion at 85% of VO_{2peak}	RER was significantly lower in L-carnitine group compared to the placebo group. Blood lactate was significantly lower after 10 min of cycling at 65% of VO_{2peak} in L-carnitine group compared to the placebo group. Power output was similar between groups. No effect in time to exhaustion.

g = grams, h = hours, wks = weeks, yrs = years

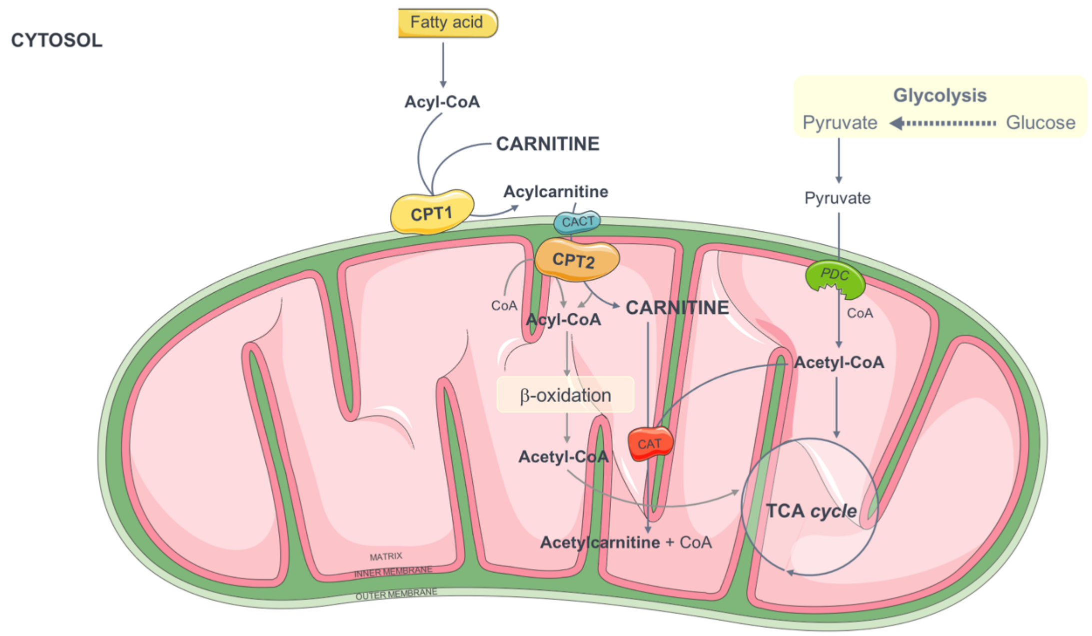

Figure 1: Roles of L-carnitine within skeletal muscle. L-carnitine shuttles long-chain fatty acids inside the mitochondria by forming acylcarnitine. This molecule is then transported in to the mitochondrial matrix by carnitine acetyltransferase I (CPT I) and carnitine acetyltransferase II (CPT II). Fatty 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 acetycarnitine and coenzyme A.

CAT, carnitine acetyltransferase; CoA, coenzyme, CPT, carnitine palmitoyltransferase, PDC, pyruvate dehydrogenase complex, TCA, tricarboxylic acid

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