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REVIEW

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The bright and the dark sides of L-carnitine supplementation: a systematic review

Angelika K. Sawicka[1], Gianluca Renzi[2] and Robert A. Olek[3*]

Abstract

Background: L-carnitine (LC) is used as a supplement by recreationally-active, competitive and highly trained athletes. This systematic review aims to evaluate the effect of prolonged LC supplementation on metabolism and metabolic modifications.

Methods: A literature search was conducted in the MEDLINE (via PubMed) and Web of Science databases from the inception up February 2020. Eligibility criteria included studies on healthy human subjects, treated for at least 12 weeks with LC administered orally, with no drugs or any other multi-ingredient supplements co-ingestion.

Results: The initial search retrieved 1024 articles, and a total of 11 studies were finally included after applying inclusion and exclusion criteria. All the selected studies were conducted with healthy human subjects, with supplemented dose ranging from 1 g to 4 g per day for either 12 or 24 weeks. LC supplementation, in combination with carbohydrates (CHO) effectively elevated total carnitine content in skeletal muscle. Twenty-four-weeks of LC supplementation did not affect muscle strength in healthy aged women, but significantly increased muscle mass, improved physical effort tolerance and cognitive function in centenarians. LC supplementation was also noted to induce an increase of fasting plasma trimethylamine-N-oxide (TMAO) levels, which was not associated with modification of determined inflammatory nor oxidative stress markers.

Conclusion: Prolonged LC supplementation in specific conditions may affect physical performance. On the other hand, LC supplementation elevates fasting plasma TMAO, compound supposed to be pro-atherogenic. Therefore, additional studies focusing on long-term supplementation and its longitudinal effect on the cardiovascular system are needed.

Keywords: Insulin-like growth factor-1, Protein kinase B, Mammalian target of rapamycin, Forkhead box O, MuRF-1, Atrogin-1, Trimethylamine-N-oxide

Background

The main function of L-carnitine (LC) is the transport of long-chain fatty acids into the mitochondrial matrix for their conversion in energy, via β-oxidation process [1]. Moreover, LC by the reaction with acetyl-CoA and maintaining the acetyl-CoA/CoA ratio in the cell regulates pyruvate dehydrogenase activity [2]. LC also plays an important role in the regulation of metabolic pathways involved in skeletal muscle protein balance: proteolysis and protein synthesis [3]. Furthermore, LC acts as anti-oxidant and anti-inflammatory compound [3]; thus, it may attenuate the exercise-induced muscle damage.

The opinion that LC supplementation does not change metabolism is based mostly on short-term supplementation protocols [4]. Recent studies demonstrate that prolonged supplementation, especially in combination with carbohydrates (CHO), may increase muscle total carnitine (TC) content in skeletal muscle [5–7]. Therefore, LC supplementation in specific conditions may affect physical performance. On the other hand, LC has been proposed as the red meat nutrient responsible for atherosclerosis promotion [8]. As a potential link between

* Correspondence: robert.olek@aol.com
[3]Department of Athletics, Strength and Conditioning, Poznan University of Physical Education, Krolowej Jadwigi 27/39, 61-871 Poznan, Poland
Full list of author information is available at the end of the article

red meat consumption and the increasing risk of cardiovascular disease, trimethylamine-N-oxide (TMAO) has been indicated [8]. Since LC is still used by the athletes [9, 10], the aim of this systematic review is to evaluate the effect of prolonged LC supplementation on metabolism/metabolic changes in healthy human subjects.

Methods

Eligibility criteria

The PICOS strategy was defined as follows: "P" (participants) human subjects, "I" (interventions) oral LC treatment, "C" (comparisons) between supplementation and placebo, supplementation and control, or pre- and post-supplementation, "O" (outcomes) muscle variables, and "S" (study design) randomized controlled trials, non-randomized controlled trials, non-randomized non-controlled trials.

Studies with the following criteria were excluded: described in languages other than English, articles without full-text availability, reviews and case reports. Subsequently, the following eligibility criteria were applied: a) healthy human subjects; b) supplementation at least for 12 weeks; c) oral LC administration; d) no drugs co-ingestion; e) no multi-ingredients supplementation.

Information sources and search

The literature was explored using the MEDLINE (via PubMed) and Web of Science databases, including all articles published from the inception up February 2020. The search was conducted using the terms: "carnitine supplementation" or "carnitine treatment" in combination with "exercise", "training", "athletic performance", "muscle strength", "muscle fatigue", "muscle damage", "muscle recovery", "muscle synthesis" or "proteolysis".

Study selection

Firstly, studies were assessed by title verification between databases (duplicates were removed). The second assessment performed by abstracts analysis, excluded studies in a language other than English, studies with lack of full text, reviews, case reports, animal studies and in-vitro studies. The last step was performed by analysis of full manuscripts based on the described above eligibility criteria.

Data collection process

The following information was compiled for each study: authors, year of publication, type of study, length of supplementation, a dose of supplementation and main effect. Lastly, the thematic analysis was carried out, to synthesize and interpret all the data that appeared from the included publications. The process of selecting papers, data collection as well as the quality assessment was performed independently by two authors (A.S., G.R.), and all disagreements were resolved by the discussion with the third author (R.O).

Results

Study selection

By the above-described search strategy, 1295 publications were identified. After the first selection, adjusted by duplicates, persisted 1024 articles. Of these, 794 were excluded after abstracts screening and identified articles in languages other than English, lack of full text or being review articles, case reports, animal or in-vitro studies. The full texts of 230 articles were screened by eligibility criteria. Finally, to the qualitative analysis were accepted 11 studies performed on healthy human subjects, treated for at least 12 weeks with LC administered orally, with no drugs or any other multi-ingredient supplements co-ingestion (Fig. 1).

Description of the included studies

Table 1 provides details and results of the 11 studies reviewed. Selected studies were published between 2002 and 2020. In the selected studies, participants were supplemented in a dose ranging from 1 g to 4,5 g per day for either 12 or 24 weeks, mostly by L-carnitine-L-tartrate (LCLT). In three studies, supplementations were combined with carbohydrates (CHO) [5–7], and in one with L-leucine [18].

Muscle carnitine content was not affected following 12 weeks of LC supplementation alone [11, 12]. On the other hand, LC supplementation in combination with CHO effectively elevated muscle TC after 12 [6] and 24 weeks [5]. Moreover, 12 weeks of supplementation alone [13], or in combination with CHO [6] promote the expression of the genes related to fatty acids and carnitine metabolism.

Twenty-four-weeks of LC supplementation alone did not affect muscle strength in healthy aged women [15], but significantly increased muscle mass, improved physical effort tolerance and cognitive function in centenarians [14].

In two studied groups of healthy aged woman, LC supplementation alone [16, 17], or in combination with L-leucine [18], induced an increase of fasting plasma TMAO levels. However, higher TMAO was not associated with determined inflammatory [16] nor oxidative stress [17] markers. Moreover, despite elevated TMAO, LC supplementation together with resistance training induced positive changes in mitochondrial DNA methylation of platelets [18].

Discussion

The present findings have been debated in the six separate paragraphs, and for a better picture of LC supplementation, other studies were also disputed.

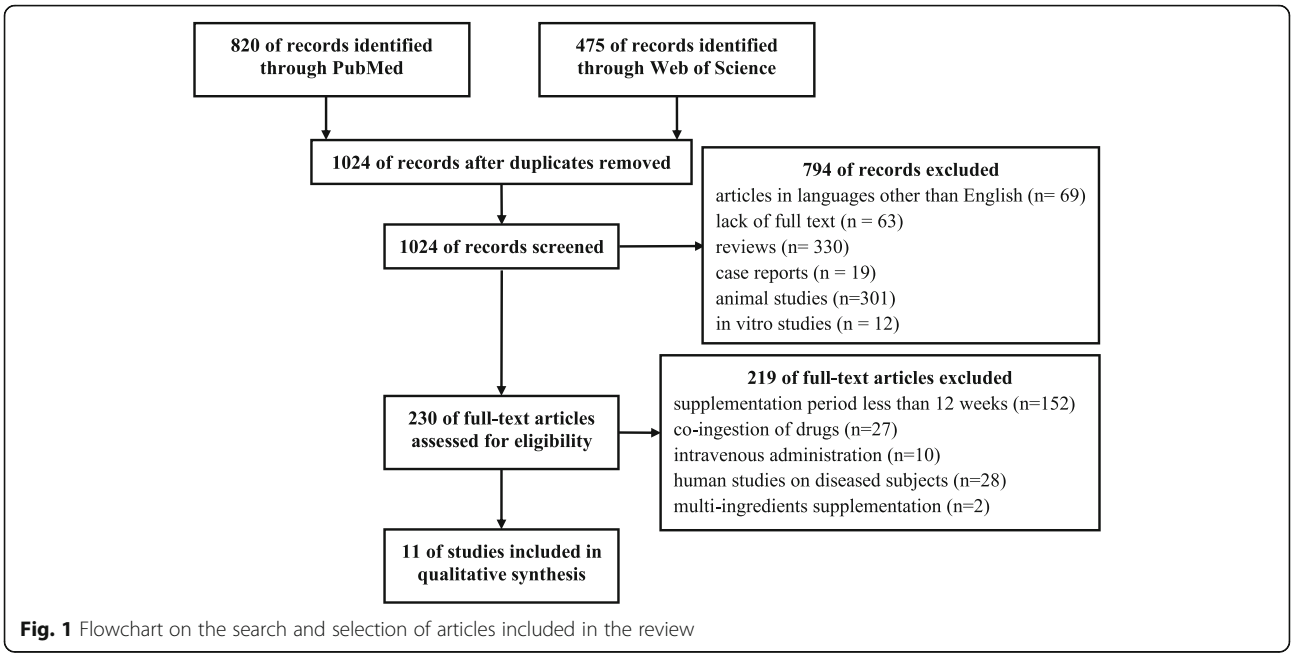

Fig. 1 Flowchart on the search and selection of articles included in the review

"Fat burner"

It has been assumed that LC supplementation, by increasing muscle carnitine content, optimizes fat oxidation and consequently reduces its availability for storage [19]. Nevertheless, the belief that carnitine is a slimming agent has been negated in the middle of 90s [20]. Direct measurements of carnitine in skeletal muscles failed to show any elevation in the muscle carnitine concentration following 14 days of 4 g/day [21], or 6 g/day [22] LC ingestion. These findings implied that LC supplementation was not able to increase fat oxidation and improve exercise performance by the proposed mechanism. Indeed, many original investigations, summarized in later review [4], indicated that LC supplementation lasting up to 4 weeks, neither increase fat oxidation nor improve performance during prolonged exercises.

Since LC concentration in skeletal muscles is higher than that of blood plasma, active uptake of carnitine must take place [23]. Stephens et al. [24] noted that 5 h steady-state hypercarnitinemia (~ 10-fold elevation of plasma carnitine) induced by the intravenous LC infusion does not affect skeletal muscle TC content. On the other hand, similar intervention in combination with controlled hyperinsulinemia (~ 150mIU/L) elevates TC in skeletal muscle by ~ 15% [24, 25]. Moreover, higher serum insulin maintained by the consumption of simple sugars resulted in augmented LC retention in healthy human subjects supplemented by LC for 2 weeks [26]. Based on these results, Authors suggested that oral ingestion of LC, combined with CHO for activation carnitine transport into the muscles, should take ~ 100 days to increase muscle carnitine content by ~ 10% [26]. This assumption has been confirmed in later studies [5–7]. These carefully conducted studies clearly showed that prolonged procedure (for ≥12 weeks) of a daily LC and CHO ingestion induced a raise of skeletal muscle TC levels [5–7], affecting exercise metabolism [5], improving performance [5] and energy expenditure [6], without altering body composition [6]. The lack of body fat stores loss may be explained by the 18% increase in body fat mass associated with CHO supplementation alone, noted in the control group [6].

Nevertheless, 12 weeks of LC supplementation 2 g/day applied without CHO, elevated muscle TC only in vegetarian but not in omnivores [12]. Neither exercise metabolism nor muscle metabolites were modified by augmented TC in vegetarian [12].

Skeletal muscle protein balance regulation

Skeletal muscle mass depends on the rates of protein synthesis and degradation. Elevated protein synthesis and attenuated proteolysis are observed during muscle hypertrophy. Both of these processes are mainly regulated by the signaling pathway: insulin-like growth factor-1 (IGF-1) – phosphoinositide-3-kinase (PI3K) – protein kinase B (Akt) – mammalian target of rapamycin (mTOR). The activation of mTOR leads to phosphorylation and activation of S6 kinases (S6Ks) and hyperphosphorylation of 4E-binding proteins (4E-BPs), resulting in the acceleration of protein synthesis. At the same time, Akt phosphorylates and inactivates forkhead box O (FoxO), thereby inhibit the responsible for proteolysis ubiquitin ligases: muscle-specific RING finger-1 (MuRF-

Table 1 Summary and results of the studies reviewed examining the LC supplementation

Studies	Participants characteristics	Study design	Supplementation dose and period	Main effect
[11]	Moderately trained male subjects ($n = 7$) age 23–25	NRNC	4 g LC/day for 3 months	Increase of TC plasma concentration after the supplementation; No change in muscle TC concentration, mitochondrial enzymes activity, physical performance and muscle fiber composition
[12]	Male vegetarians ($n = 16$) and omnivores (C) ($n = 8$) age 18–40	NRC	2 g LCLT /day for 12 weeks	Increase of TC plasma concentration after the supplementation and muscle TC concentration only in vegetarians; No change in physical performance and muscle metabolism either in omnivores or vegetarians.
[13]	Middle aged untrained male subjects (S $n = 12$; P $n = 12$) age not reported (both groups involved in endurance training; 3x/ week)	RC	2 g LCLT /day for 12 weeks	Increase of TC plasma concentration after the supplementation; Plasma triacylglycerols and free fatty acids not affected by training or supplementation; Training resulted in an increase in the mRNA expression of genes coding proteins involved in long chain fatty acid transport in white blood cells, LC supplementation enhanced the effect on gene expression
[6]	Non-vegetarian, male recreational athletes (S n = 6; P $n = 6$) age 28 ± 2 (S); 25 ± 2 (P)	RC	2 g LCLT + 80 g CHO /day for 12 weeks	Increase in muscle TC concentration after LC supplementation; Upregulation of seventy-three genes relating to fuel metabolism in LC vs. control; Higher exercise energy expenditure after LC supplementation; No change in carnitine palmitolytransferase 1 activity; Body mass and whole-body fat mass increased in control, but did not change in LC supplemented
[5]	Non-smoking, non-vegetarian recreational athletes (S $n = 7$; P $n = 7$) age 26 ± 2	RC	2 g LCLT + 80 g CHO /day for 24 weeks	Increase in muscle TC concentration after LC supplementation; Lower muscle glycogen utilization during low intensity exercise, lower lactate production during high intensity exercise, higher work output during a 30 min 'all-out' exercise performance test in LC supplemented group;
[7]	Healthy, non-vegetarian, untrained males (S $n = 7$; P $n = 7$) age 23 ± 2 (both groups involved in HIIT; 3x/week)	RC	2.25 g LCLT + 80 g CHO /day for 24 weeks	Muscle TC concentration tend to increase after LC supplementation ($p = 0.06$ vs. pre-supplementation); Skeletal muscle adaptations to training not augmented by elevated muscle carnitine availability;
[14]	Centenarians (S $n = 27$; P $n = 27$) age 100–106	RC	2 g LC/day for 24 weeks	Increase of TC plasma concentration after the supplementation; Fat mass reduction, muscle mass elevation, physical effort tolerance and cognitive function improvement in LC supplemented group
[15]	Healthy women (S $n = 11$; P $n = 9$) age 65–70	RC	1.5 g LCLT /day for 24 weeks	Increase of free carnitine plasma concentration after the supplementation; No changes in body composition, skeletal muscle strength and IGF-1 after LC supplementation
[16]	Healthy women (S $n = 11$; P $n = 9$) age 65–70	RC	1.5 g LCLT /day for 24 weeks	Increase of plasma TMAO concentration after the supplementation; No changes in serum C-reactive protein, interleukin-6, tumor necrosis factor-α, L-selectin, P-selectin, vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and lipid profile after LC supplementation
[17]	Healthy women (S $n = 11$; P $n = 9$) age 65–70	RC	1.5 g LCLT /day for 24 weeks	No changes in plasma GBB or serum ox-LDL, myeloperoxidase, protein carbonyls, homocysteine, and uric acid concentrations
[18]	Healthy aged women (S $n = 12$; P $n = 13$; C $n = 12$) age 67 ± 3 (all groups involved in resistance training 3x/week)	RC	1 g LCLT + 3 g L-leucine/day for 24 weeks	Increase of plasma TMAO concentration after the supplementation; Increase of D-loop methylation in platelets of LC supplemented

Groups: *C* control; *S* supplemented; *P* placebo; Study design: *RC* randomized controlled; *NRC* non-randomized controlled; *NRNC* non-randomized non-controlled; *LCLT* L-carnitine-L-tartrate; *HIIT* high-intensity interval training

1) and muscle atrophy F-box protein (atrogin-1), (for review see [27–29]).

The association between LC supplementation and the regulation of metabolic pathways involved in muscle protein balance have been shown in several animal studies (Fig. 2) [30–35]. Four weeks of LC supplementation in rats increased plasma IGF-1 concentration [33]. Elevated circulating IGF-1 led to an activation of the IGF-1–PI3K–Akt signalling pathway, causing augmented mTOR phosphorylation and higher phospho-FoxO/total FoxO ratio in skeletal muscle of LC supplemented rats [33]. FoxO inactivation attenuated MURF-1 expression in *quadriceps femoris* muscle of supplemented rats (compared to control) [33]. Moreover, LC administrated for 2 weeks suppresses atrogin-1 messenger RNA (mRNA) level in suspended rats' hindlimb [35], and only 7 days of LC administration downregulates MuRF-1 and atrogin-1 mRNAs reducing muscle wasting in a rat model of cancer cachexia [32]. All these findings together might suggest that LC supplementation protect muscle from atrophy, especially in pathophysiological conditions.

In fact, administration of acetyl-L-carnitine 3 g/day for 5 months in HIV-seropositive patients induced ten-fold increase in serum IGF-1 concentration [36]. Conversely, neither 3 weeks LC supplementation in healthy, recreationally weight-trained men [37], nor 24 weeks LC supplementation in aged women [15] did not affect circulating IGF-1 level concentration. Various effects might be due to different IGF-1 levels; significantly lower in the HIV-seropositive patients than in healthy subjects [38]. Additionally, 8 weeks of LC supplementation in healthy older subjects, did not change total and phosphorylated mTOR, S6K and 4E-BP proteins level of *vastus lateralis* muscle [39]. It must be highlighted that rat skeletal muscle TC increases ~ 50–70% following 4 weeks of LC supplementation [33, 34], whereas comparable elevation has never been observed in human studies, even after 24 weeks of supplementation [5, 7].

Body composition

These findings altogether suggest that prolonged LC supplementation might affect body composition in specific conditions.

Obesity

A recent meta-analysis, summarized studies focused on LC supplementation for a prolonged time (median 3 months) [40]. Pooled results demonstrated a significant reduction in weight following LC supplementation, but the subgroups analysis revealed no significant effect of LC on body weight in subjects with body mass index (BMI) below 25 kg/m^2. Therefore, authors suggested that LC supplementation may be effective in obese and overweight subjects. Surprisingly, intervention longer than 24 weeks showed no significant effect on BMI [40].

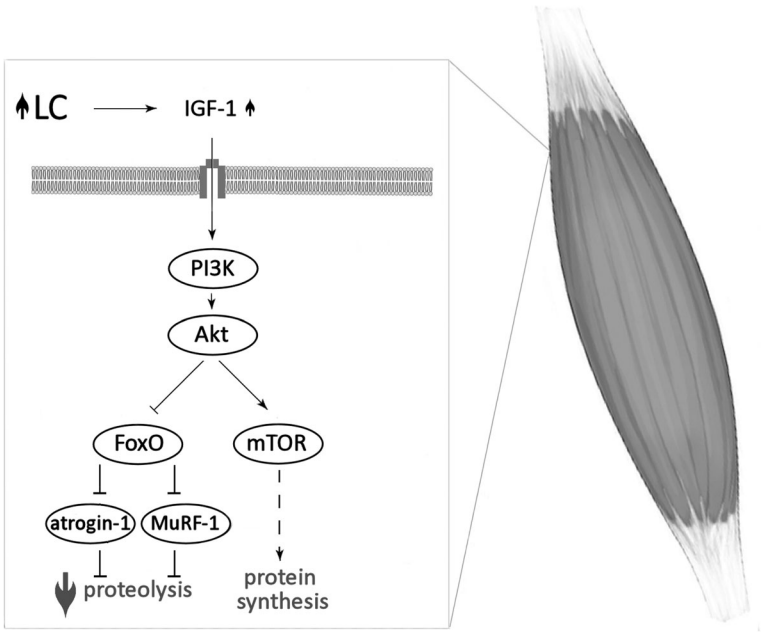

Fig. 2 The association between LC supplementation and the regulation of metabolic pathways involved in muscle protein balance. L-carnitine (LC); insulin-like growth factor-1 (IGF-1); phosphoinositide-3-kinase (PI3K); protein kinase B (Akt); mammalian target of rapamycin (mTOR); forkhead box O (FoxO); muscle-specific RING finger-1 (MuRF-1); muscle atrophy F-box (atrogin-1); increase (↑); decrease (↓); activation (→); inactivation (⊣)

Training

It has been assumed that a combination of LC supplementation with increased energy expenditure may positively affect body composition. However, either with aerobic [41, 42] or resistance [43] training, LC supplementation has not achieved successful endpoint. Six weeks of endurance training (five times per week, 40 min on a bicycle ergometer at 60% maximal oxygen uptake) together with LC supplementation (4 g/day) does not induce a positive effect on fat metabolism in healthy male subjects (% body fat 17.9 ± 2.3 at the beginning of the study) [41]. Similarly, lack of LC effect has been reported in obese women [42]. Eight weeks of supplementation (2 g/day) combined with aerobic training (3 sessions a week) had no significant effects on body weight, BMI and daily dietary intake in obese women [42].

In the recent study, LC supplementation 2 g/day has been applied in combination with a resistance training program (4 days/week) to healthy men (age range 18–40 y.o.), for 9 weeks [43]. Body composition, determined by dual energy X-ray absorptiometry, indicated no significant effect in fat mass and fat-free mass due to supplementation. Moreover, LC administration did not influence bench press results. The number of leg press repetitions and the leg press third set lifting volume increased in the LC group compared to the placebo group [43]. Different LC effect in the limbs may be associated with the higher rates of glycogenolysis during arm exercise at the same relative intensity as leg exercise [44].

Sarcopenia

Aged people have accelerated protein catabolism, which is associated with muscle wasting [45]. LC could increase the amount of protein retention by inhibition of the proteolytic pathway. Six months of LC supplementation augmented fat free mass and reduced total body fat mass in centenarians [14]. Such effect was not observed in elder women (age range 65–70 y.o.) after a similar period of supplementation [15]. The effectiveness of LC supplementation may result from the age-wise distribution of sarcopenia. The prevalence of sarcopenia increased steeply with age, reaching 31.6% in women and 17.4% in men older than 80 years [46]. In subjects below 70 years presarcopenia, but not sarcopenia symptoms were noted [46].

Oxidative imbalance and muscle soreness

Muscle damage may occur during exercise, especially eccentric exercise. In the clearance of damaged tissues assist free radicals produced by neutrophils. Therefore, among other responses to exercise, neutrophils are released into the circulation. While neutrophil-derived reactive oxygen species (ROS) play an important role in breaking down damaged fragments of the muscle tissue, ROS produced in excess may also contribute to oxidative stress (for review see [47, 48].

Based on the assumption that LC may provide cell membranes protection against oxidative stress [49], it has been hypothesized that LC supplementation would mitigate exercise-induced muscle damage and improve post-exercise recovery. Since plasma LC elevates following 2 weeks of supplementation [21, 22], short protocols of supplementation may be considered as effective in attenuating post-exercise muscle soreness. The findings indicated that 3 weeks of LC supplementation, in the amount 2-3 g/day, effectively alleviated pain [50–53]. It has been shown, through magnetic resonance imaging technique that muscle disruption after strenuous exercise was reduced by LC supplementation [37, 51]. This effect was accompanied by a significant reduction in released cytosolic proteins such as myoglobin and creatine kinase [50, 52, 53] as well as attenuation in plasma marker of oxidative stress - malondialdehyde [51, 53, 54]. Furthermore, 9 weeks of LC supplementation in conjunction with resistance training revealed a significant increase of circulating total antioxidant capacity and glutathione peroxidase activity and decrease in malondialdehyde concentration [43].

Risks of TMAO

In 1984 Rebouche et al. [55], showed that rats, orally receiving radiolabeled LC, metabolized it to γ-butyrobetaine (up to 31% of the administered dose, present primary in feces) and TMAO (up to 23% of the administered dose, present primary in urine). On the contrary, these metabolites were not produced by the rats receiving the isotope intravenously and germ-free rats receiving the tracer orally, suggesting that orally ingested LC is in part degraded by the gut's microorganisms [55]. Similar observations were noted in later human studies [56, 57], with the peak serum TMAO observed within hours following oral administration of the tracer [56]. Prolonged LC treatment elevates fasting plasma TMAO [16–18, 58, 59]. Three months of oral LC supplementation in healthy aged women induced ten-fold increase of fasting plasma TMAO, and this level remained elevated for the further 3 months of supplementation [16]. Four months after cessation of LC supplementation, plasma TMAO reached a pre-supplementation concentration, which was stable for the following 8 months [60].

In 2011 Wang et al. [61] suggested TMAO as a pro-atherogenic factor. Since diets high in red meat have been strongly related to heart disease and mortality [62], LC has been proposed as the red meat nutrient responsible for atherosclerosis promotion [8]. As a potential link between red meat consumption and the increasing risk of cardiovascular disease, TMAO has been indicated

[8]. Numerous later studies have shown the association between increased plasma TMAO levels with a higher risk of cardiovascular events [63–66]. The recent meta-analyses indicated that in patients with high TMAO plasma level, the incidence of major adverse cardiovascular events was significantly higher compared with patients with low TMAO levels [67], and that all-cause mortality increased by 7.6% per each 10 μmol/L increment of TMAO [68].

Since red meat is particularly rich in LC [69], dietary intervention in healthy adults, indicated a significant increase in plasma and urine TMAO levels following 4 weeks of the red meat-enriched diet [70]. The rise of plasma TMAO was on average three-fold compared with white meat and non-meat diets [70]. Conversely, habitual consumption of red, processed or white meat did not affect plasma TMAO in German adult population [71]. Similarly, a minor increase in plasma TMAO was observed following red meat and processed meat consumption in European multi-center study [72].

In the previous century, the underlined function of TMAO was the stabilization of proteins against various environmental stress factors, including high hydrostatic pressure [73]. TMAO was shown as widely distributed in sea animals [74], with concentration in the tissue increasing proportionally to the depth of the fishes natural environment [75]. Consequently, fish and seafood nutritional intake has a great impact on TMAO level in the human body [76], significantly elevating also plasma TMAO concentration [72]. Therefore, link between plasma TMAO and the risk of cardiovascular disease [8] seems like a paradox, since more fish in the diet reduces this risk [77].

Not only dietary modification may affect TMAO plasma levels. Due to TMAO excretion in urine [56, 57], in chronic renal disease patients, TMAO elimination from the body fails, causing elevation of its plasma concentration [78]. Therefore, higher plasma TMAO in humans was suggested as a marker of kidney damage [79]. It is worthy to note that cardiovascular disease and kidney disease are closely interrelated [80] and diminished renal function is strongly associated with morbidity and mortality in heart failure patients [81]. Moreover, decreased TMAO urine excretion is associated with high salt dietary intake, increasing plasma TMAO concentration [82].

The relation between TMAO and chronic disease can be ambiguous, involving kidney function [79], disturbed gut-blood barrier [83], or flavin-containing monooxygenase 3 genotype [84]. Thus, whether TMAO is an atherogenic factor responsible for the development and progression of cardiovascular disease, or simply a marker of an underlined pathology, remains unclear [85].

Adverse effects

Carnitine preparations administered orally can occasionally cause heart-burn or dyspepsia [86]. No adverse events associated with LC administration were recorded at a dose 6 g/day for 12 months of supplementation in the patients with acute anterior myocardial infarction [87], or at a dose 1.274 g/day (range 0.3–3 g/day) and duration 348 days (range 93–744 days) in patients with liver cirrhosis [88]. Summarizing the risk associated with LC supplementation Hathcock and Shao [89] indicated that intakes up to 2 g/day are safe for chronic supplementation.

Although the optimal dose of LC supplementation for myocardial infarction is 3 g/day in terms of all-cause mortality [90], even lower LC intake elevates fasting plasma TMAO [16–18, 58, 59], which is ten-fold higher than control after 3 months of supplementation [16, 17]. It is worthy to mention that Bakalov et al. [91] analyzing European Medicine Agency database of suspected adverse drug reaction, noticed 143 cases regarding LC.

Strengths and limitations

The strength of this review is a focus on the period of LC treatment, very important aspect often missed in many articles dealing with this supplement. To date, only few studies have examined the effects of LC supplementation for at least 12 weeks, which is, on the other hand, the main limitation of the current review. This limitation is also magnified by the varied design of the studies available including different supplementation protocols and outcome measures. There is also a high degree of heterogeneity among participants of the analyzed studies. Therefore, the results should be taken with caution, and more research is required before definitive recommendations.

Conclusions

Lasting for several years opinion that LC supplementation does not change metabolism, especially exercise metabolism, is based mostly on short-term supplementation protocols. Nevertheless, LC is still used by elite [9] and sub-elite [10] athletes. Recent studies suggest that LC supplementation may elevate muscle TC content; therefore, modify muscle fuel metabolism and performance during the exercise. Due to insulin-mediated LC transport to the muscle, oral administration regimen should be combined with CHO. Because of LC poor bioavailability, it is likely that the supplementation protocol would take at least 3 months. Shorter period of supplementation may be effective in prevention of exercise-induced muscle damage, but not metabolic changes.

On the other hand, it is also clear that prolonged LC supplementation elevates fasting plasma TMAO [16–18, 58, 59], compound supposed to be pro-atherogenic [61]. Therefore, additional studies focusing on long-term

supplementation and its longitudinal effect on the TMAO metabolism and cardiovascular system are needed.

Abbreviations

LC: L-carnitine; TC: Total carnitine; TMAO: Trimethylamine-N-oxide; CHO: Carbohydrates; IGF-1: Insulin-like growth factor-1; PI3K: Phosphoinositide-3-kinase; Akt: Protein kinase B; mTOR: Mammalian target of rapamycin; S6K: S6 kinase; 4E-BP: 4E-binding protein; FoxO: Forkhead box O; MuRF-1: Muscle-specific RING finger-1; atrogin-1: Muscle atrophy F-box; mRNA: Messenger RNA; BMI: Body mass index; ROS: Reactive oxygen species

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Authors' contributions

Conceptualization: R.O.; Writing-original draft preparation: A.S., G.R. and R.O.; The authors declare that the content of this paper has not been published or submitted for publication elsewhere. All authors have read and agreed to the published version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Human Physiology, Faculty of Health Sciences, Medical University of Gdansk, 80-210 Gdansk, Poland. [2]University of Camerino, 62032 Camerino, Italy. [3]Department of Athletics, Strength and Conditioning, Poznan University of Physical Education, Krolowej Jadwigi 27/39, 61-871 Poznan, Poland.

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