

L-carnitine as primary or adjuvant treatment in infertile patients with varicocele. A systematic review

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Summary *Background: Varicocele has been found to impair the function of the epididymis resulting in subfertility whereas the varicocelectomy can resolve the phenomenon. L-carnitine is regarded as a biomarker for the function of the epididymis and has been found in reduced concentrations in infertile patients of various causes, including infertile men with varicocele. It seems that L-carnitine and varicocele share clinical significance and the area of research looks promising.*

Objective: To identify the role of L-carnitine in the treatment of varicocele.

Materials and methods: A systematic search was performed in Pubmed/Medline with the terms (L-carnitine) and (varicocele) and (L-carnitine) and (varicocelectomy). Inclusion criteria were studies reported outcomes of L-carnitine administration alone or in duet, as primary or adjuvant treatment to varicocele. Exclusion criteria were non-English language and animal studies. Studies using L-carnitine as part of a panel of therapeutic agents were avoided.

Results: Only four suitable studies were identified for discussion. In one randomized study, the combination of L-carnitine and cinnoximac improved semen parameters in patients with non-high-grade varicocele compared to L-carnitine alone and had a favourable effect on pregnancy rates but the effect of grade is unknown. In another study, as an adjuvant treatment to varicocelectomy, L-carnitine showed no clear benefit. Finally, in comparison to surgery, the results are inconclusive; two studies showed some benefit might be expected in low-grade or subclinical varicocele, but surgery appears superior.

Conclusions: The evidence regarding the role of L-carnitine as a primary or adjuvant treatment of varicocele is sparse. The pathophysiological significance of L-carnitine implicates a potential role of the molecule in the management of varicocele, but the evidence so far is controversial for any recommendations. L-carnitine might be taken into consideration in selected cases; however, further search is needed in order the optimal role of L-carnitine in infertile patients with varicocele to be clarified.

KEY WORDS: Varicocele; Male infertility; L-carnitine; Antioxidants; Varicocelectomy.

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INTRODUCTION - BACKGROUND

Varicocele is considered one of the most common treatable causes of male infertility (1). The interventional or surgical approach is considered the standard of care for the condition in case of infertility due to favourable outcomes regarding improvement in semen parameters and pregnancy rates (2). In modern era, research has also focused on the varicocele-induced oxidative stress and reduction in antioxidant capacity which results in impaired spermatogenesis, broadening new horizons in the treatment of the condition (3, 4). Antioxidative treatment is well-established in idiopathic infertility and oligoasthenoteratospermia (OAT), albeit the results still conflicting and the optimal agents or combination still lacking (5). Among the investigated agents, L-carnitine (LC) has shown effectiveness on ameliorating oxidative stress, improving semen parameters in infertile patients (6-9). Additionally, the molecule has a significant physiological role and the measurement of seminal L-carnitine is used as biomarker for the assessment of epididymal function in patients with various fertility issues including varicocele (10, 11).

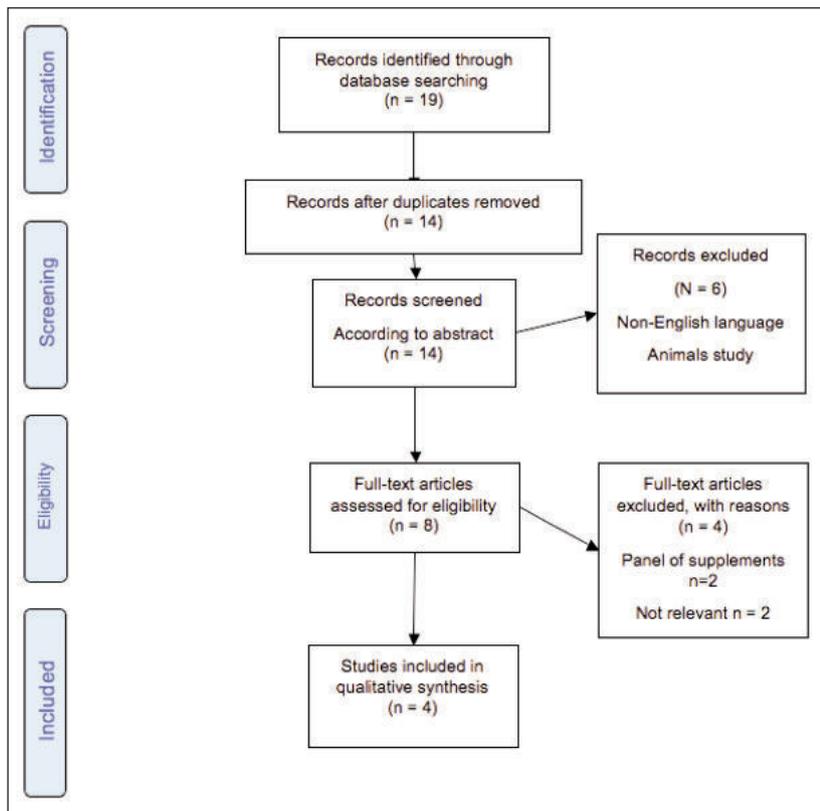
The measurement of L-carnitine in the semen is meaningful and clinically relevant as a positive correlation between seminal carnitine levels and several semen parameters including motility, concentration and DNA quality has been shown in infertile patients with varicocele (12). All the above render LC as a potent biomarker during the evaluation of infertile patients with varicocele and as a potential target in the treatment of such patients as well. In this review, we explore the role of LC in the potential management of varicocele.

MATERIALS AND METHODS

We performed a systematic literature search using the advanced search engine in PubMed/Medline with the terms (L-carnitine) and (varicocele) and (L-carnitine) and (varicocelectomy).

The results were checked for duplicates in Mendeley. Our search targeted studies reporting conclusions relating to

Figure 1.
PRISMA 2009 Flow Diagram.



the role of carnitine management of varicocele. Only studies using L-carnitine alone or in duet were included and studies reporting results with combination of multiple antioxidants were avoided.

Animal studies, case reports and articles in non-English language were excluded; reviews were also excluded from the literature search but were screened independently for the identification of other sources.

The flowchart of our strategy is presented on Figure 1. The risk of bias assessment of the selected studies is illustrated on Figure 2.

Figure 2.
Risk of bias of the selected studies.



RESULTS (Table 1)

Performance of L-carnitine in infertile patients with varicocele as sole treatment

One study was identified reporting the benefit of LC administration in semen parameters of infertile patients with varicocele-induced OAT. *Cavallini et al.* randomized patients into 3 groups, group 1 given placebo only, group 2 given oral LC (2 g/d)/acetyl-L-carnitine (1 g/d) and placebo suppository and group 3 given oral LC and suppository cinnoxicam 30 mg every 4 days; the medication were given for a total duration of 6 months whereas the varicocele was graded according to the severity of venous reflux into 5 grades, with grades 1-2 corresponding to subclinical varicocele and grades 3-5 corresponding to clinical grades I, II and III respectively (13). The authors observed that the combination group had significantly increased sperm parameters at 3 and 6 months compared to other groups in patients with grade 1 to 4 whereas the effect was durable as long as patients were on the medication; on the other hand, no treatment made any difference in grade 5 varicoceles. Thus,

the authors concluded that the combination of LC and cinnoxicam suppositories proved a reliable treatment for low-grade varicoceles in terms of semen parameters but not efficient for high grades; notably, the pregnancy rates were also raised in group 3 but there was no special comment regarding the varicocele grade contribution (13).

Performance of L-carnitine in comparison to varicocelectomy

Two studies reported outcomes of varicocelectomy compared to administration of LC.

In one study, Sofimajidpour et al allocated 62 patients with a mean age of 29 years and mean infertility duration of 3.3 years with clinical varicocele grade II or more into two groups; thirty-one patients were administrated an oral dose of 250 mg LC four times a day for six months and 31 patients underwent varicocelectomy (14). Both groups showed significant improvement in semen parameters including sperm count, motility, morphology and semen volume while no difference was observed between groups (14).

Notably, the study was not randomized and the groups differed significantly in terms of clinical grade (the 87.1% of the participants in the medicinal group had grade II varicocele in comparison to 25.8% of patients in the

Table 1.
Summarized data of the studies.

	Scope	Type of clinical trial	Number of participants	Main outcome/conclusions	Comments
<i>Cavallini et al. (2004)</i>	Placebo vs LC alone vs LC and cinnoximac on the improvement of semen parameters in infertile patients with idiopathic OAT and infertile patients with OAT and various grades of VC (including SV)	Prospective/ randomized	195 patients into 3 groups *	Significant improvement in grades I-IV for drug combination but no treatment was effective in grade V	The higher the grade, the lower the benefit of drug therapy; combination group had increased pregnancy rates, but the contribution of grade is unknown
<i>Sofimajidpour et al. (2016)</i>	Varicocelectomy vs LC alone on the improvement of semen parameters of infertile patients with varicocele of various clinical grades	Prospective/ non-randomized (patient preference)	62 patients into 2 groups	No significant difference between groups	Imbalance of grade contribution between groups as most patients at medical group had grade II and most patients at surgical group had grade III varicocele
<i>JT Seo et al. (2008)</i>	Observation vs varicocelectomy vs LC alone on infertile patients with SV	Retrospective	143 patients into 3 groups	Varicocelectomy outnumbered LC monotherapy and observation in both semen parameters and pregnancy rates	LC administration was better vs observation in terms of pregnancy rates but inferior to varicocelectomy
<i>Pourmand et al. (2014)</i>	Varicocelectomy alone vs Varicocelectomy plus adjuvant LC on improvement of semen parameters and DNA in infertile patients with varicocele	Prospective/(block) Randomized	100 patients into 2 groups	No statistically significant improvement in terms of parameters and DNA damage	Lower dose than used in other studies; trend in improvement of DNA damage; longer follow-up might be required (> 6 months)

LC: L-carnitine; OAT: oligoasthenoazoospermia; VC: varicocele; SV: subclinical varicocele; * varicocele group.

surgery group); therefore, it seems that LC supplementation might be an alternative to surgery in infertile patients with grade II varicocele in terms of semen parameters (14). In a retrospective study of 143 infertile patients with left subclinical varicocele, the authors had allocated the participants into 3 groups according to their preference: a surgery group was treated with microsurgical varicocelectomy, a medical group with 3 g of LC orally for at least 6 months and an observation group including patients deciding no treatment (15). The operation increased the sperm count significantly whereas the pregnancy rate raised to 60%; on the contrary, the LC administration did not offer any benefit in terms of semen parameters but the pregnancy rate was 34.5% differing significantly to observation group (18.7%) (15).

Performance of L-carnitine as adjuvant treatment to varicocelectomy

Pourmand et al randomized 100 infertile patients with clinical and subclinical varicocele and dyspermia into two groups; the first group underwent varicocelectomy alone whereas patients in the second group were given adjuvant 750-mg oral LC a day for 6 months (16). The study failed to show any benefit of the adjuvant administration of the agent as neither the semen parameter improvement nor DNA damage reduction differed significantly in the patients underwent combined treatment in comparison to the surgery alone group; however, the slope of improvement for morphology and motility was better in the combination treatment group (16).

DISCUSSION

We decided to investigate the role of LC in the management of varicocele for two main reasons. Firstly, the epi-

didymis is considered the main supply of LC to the semen, providing around the 95% of the total amount and this is why seminal LC has been proposed as a marker for the assessment of the functional capacity of the organ (17, 18). The finding is significant as LC acts as a co-factor for the mitochondrial transport and the subsequent oxidation of fatty acids and phospholipids which are used by the epididymal spermatozoa as a substantial source of energy (19). Subsequently, a positive correlation between seminal plasma total carnitine with total sperm count and morphology has been reported, findings suggesting that the determination of seminal carnitine levels may be a useful test in evaluation of male fertility (20), (21). Varicocele has been shown to impair the function of the accessory glands including the epididymis resulting in impaired semen quality (22). Such observations come in accordance with experimental data showing that the induction of varicocele causes impairment in the epididymal microenvironment resulting in reduced epididymal carnitine levels and subsequent hypoxia, increased apoptosis and possible subsequent infertility (23). Moreover, the beneficial effect of varicocelectomy on the epididymal function is reflected as an increase of epididymis-specific proteins such as alpha-glucosidase along with the improvement in semen parameters (24). An intriguing point is that seminal L-carnitine has been reported to be reduced in infertile patients with (low-grade) varicocele and normal semen parameters; the observation is meaningful as it shows that varicoceles might impair epididymal function and cause infertility even if this is not profound in conventional spermogram, whereas LC could be used to unmask the underlying pathology and facilitate management (25). Secondly, the recent years the increased use of antioxidants as empirical treatment for several condi-

tions including male infertility has given birth to a phenomenon called “*antioxidant paradox*”, which is defined as the unresponsiveness of the body despite the administration of large doses of dietary antioxidants (26). This paradoxical phenomenon along with the possibility of increased toxicity due to excessive use of antioxidants and the harming results of reductive stress have raised concerns for more accurate therapies and specific guidelines in patients suffering from infertility (27). Therefore, we focused our search on LC alone or in dual combination as the molecule has physiological significance and we reviewed its clinical relevance as therapeutic agent.

The performance of LC in infertile patients with varicocele was reported in one randomized study and the authors concluded that the combination of the agent along with cinnoxicam was proven effective for subclinical and low-grade varicoceles in comparison to LC alone in terms of semen parameters; however, no treatment was efficient for high grades (13). If the varicocele grade affects the outcome of conservative treatment should be a matter of future research as the evidence is sparse. In a double-blind, placebo-controlled study, the combination of L-carnitine, fumarate, 5 acetyl-L-carnitine, fructose, CoQ10, vitamin C, zinc, folic acid and vitamin B12 for 6 months significantly improved the total sperm count and total and progressive motility in varicocele patients irrespective of grade; however, the pregnancy rate was not the end point in the study and cannot be assessed (28). In another study, 20 infertile patients with grade I varicocele were given multivitamins LC, vitamin C, coenzyme Q10, vitamin E, vitamin B9, vitamin B12, zinc, selenium and a significant improvement in sperm DNA quality and total sperm count was seen but other semen parameters were not affected (29). Patients with low-grade varicoceles might gain some benefit from the administration of LC in combination with other agents but future studies should explore the effect of conservative treatment on pregnancy rates especially in correlation with clinical grades.

In terms of comparison with standard of care of varicocelectomy, we identified two studies whom the conclusions should be examined carefully; none of the studies were randomized and one study had significant differences between the compared groups (14). Nevertheless, in the latter study, treating grade II varicocele conservatively with LC had similar results with treating grade III varicocele surgically and the authors concluded that conservative management could be an alternative to surgery in grade II varicoceles (14). In the study by *Seo et al*, treating subclinical varicocele with LC results in inferior pregnancy rates comparing to surgery but the performance was better than the observation (15). The observation comes in accordance with results from meta-analysis that subclinical varicocelectomy has some benefit in male infertility (30). Also, it seems that LC could be an alternative option in infertile patients with non-high-grade varicoceles, but the level of evidence is low. Last but not least, if LC is an alternative to surgery in low-grade disease needs to be clarified in future, prospective, randomized studies.

Regarding the role of adjuvant LC in patients undergoing varicocelectomy one randomized study was identified which showed no clear benefit; however, there was a

trend in favour of adjuvant treatment for motility and morphology (16). Similarly, other agents like ascorbic acid have been tested in the same manner with LC showing similar results (31). Although not fully relevant to humans, experimental data have shown that adjuvant treatment with LC may show significant benefit. In one study, Akdemir et al randomized 42 male rats into 7 groups comparing the effects of different varicocelectomy techniques with or without adjuvant LC on spermatogenesis and histopathological changes in testicular tissue (32). The authors observed that varicocelectomized rats treated with testicular non-artery sparing varicocelectomy and adjuvant LC administration had significantly increased mRNA expression levels of factors inducing the spermatogenesis comparing to other groups; additionally, in this group of patients the germ cells displayed almost total normalization in their cellular organisation (32). The discrepancy between the experimental studies and human cohorts might be associated with the nature of the condition as in experiments the varicocele is an acute phenomenon while in humans the varicocele represents a chronic disease with long-standing effects on the germ epithelium. Although this field is still unexplored, an effort to expand the efficacy of the surgery might be beneficial for some patients. A combined approach could help downgrade the indication in less invasive assisted-reproduction techniques, as this is the case with varicocelectomy in both clinical and subclinical forms (33). In that terms, adjuvant antioxidant treatment might be beneficial increasing the fatherhood chances and reducing the cost as well. If LC can act this role, it needs to be clarified with future research.

CONCLUSIONS

LC has a significant physiological role in male reproductive system and its usage sounds promising when evaluating infertile patients with varicocele. As a therapeutic agent, it seems that LC might be used in selected patients, but it cannot replace interventions whereas the level of evidence to support the agent as adjuvant treatment or monotherapy in infertile patients with varicocele is low. Future, randomized studies should investigate the optimal role of LC in the management of patients with varicocele.

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