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SYSTEMATIC REVIEW

Meta-analysis of the efficacy and safety of L-carnitine and N-acetylcysteine monotherapy for male idiopathic infertility

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Abstract

Background: Oral antioxidants especially L-carnitine (LC) and N-Acetylcysteine (NAC) are commonly used as the drug treatment method for idiopathic male infertility (IMI). **Methods**: Randomized controlled trials (RCTs) of LC and NAC monotherapy for IMI were searched systematically by using MEDLINE, EMBASE and the Cochrane Controlled Trials Register. The reference lists of retrieved studies were also perused. We analyzed the sperm concentration, normal morphology, sperm motility, and ejaculation volume. **Results**: Seven Randomized controlled trials were included. Four trials compared the efficacy of LC with placebo, and three trials compared the efficacy of NAC with placebo. In the efficacy analysis, LC increased sperm concentration ($p < 0.001$), normal morphology ($p = 0.03$), and sperm motility ($p = 0.02$); NAC improved the first three indicators while also increasing ejaculation volume ($p = 0.002$). In hormone level analysis, LC increased serum testosterone levels ($p < 0.001$), but the changes in other hormone levels were not statistically significant. **Conclusions**: Both LC and NAC can improve sperm motility, sperm concentration, and normal morphology, and increase serum testosterone concentration, but have no significant effect on other serum hormones. **The PROSPERO Registration**: CRD42024552120.

Keywords

L-carnitine; N-acetylcysteine; Antioxidant; Idiopathic male infertility; Randomized controlled trials; Meta-analysis

Meta-análisis de la eficacia y seguridad de la monoterapia con L-carnitina y N-acetilcisteína para la infertilidad masculina idiopática

Resumen

Antecedentes: Los antioxidantes orales, especialmente la L-carnitina (LC) y la N-Acetilcisteína (NAC), se utilizan comúnmente como método de tratamiento farmacológico para la infertilidad masculina idiopática (IMI). **Métodos**: Se realizaron búsquedas sistemática de ensayos controlados aleatorios (RCTs) de monoterapia con LC y NAC para IMI utilizando MEDLINE, EMBASE y Cochrane Controlled Trials Register. También se revisaron las listas de referencias de los estudios recuperados. Analizamos la concentración de esperma, la morfología normal, la vitalidad del esperma y el volumen de eyaculación. **Resultados**: Se incluyeron siete ensayos controlados aleatorios. Cuatro ensayos compararon la eficacia de LC con placebo, y tres ensayos compararon la eficacia de NAC con placebo. En el análisis de eficacia, LC aumentó la concentración de esperma ($p < 0.001$), morfología normal ($p = 0.03$) y vitalidad del esperma ($p = 0.02$); NAC mejoró los tres primeros indicadores y también aumentó el volumen de eyaculación ($p = 0.002$). En el análisis del nivel hormonal, LC aumentó los niveles de testosterona sérica ($p < 0.001$), pero los cambios en otros niveles hormonales no fueron estadísticamentes significativos. **Conclusiones**: Tanto LC como NAC pueden mejorar la motilidad del esperma, la concentración de esperma y la morfología normal, y aumentar la concentración de testosterona sérica, pero no tienen un efecto significativo en otros hormonas séricas. **El Registro de PROSPERO**: CRD42024552120.

Palabras Clave

L-carnitina; N-acetilcisteína; Antioxidante; Infertilidad masculina idiopática; Ensayos controlados aleatorios; Meta-análisis

1. Introduction

As of 2021, infertility has become a problem affecting 8%–12% of couples globally, with male factors accounting for approximately 50% [1, 2]. The causes of male infertility vary, and congenital, acquired or idiopathic factors may all affect the production of sperm. Idiopathic infertility refers to male infertility without a clear cause, accounting for approximately 30%–45% [1, 3].

According to reports, oxidative stress (OS) is associated with 30%–40% of unexplained male infertility [4] and approximately 80% of idiopathic male infertility (IMI) cases [5, 6]. Excessive reactive oxygen species (ROS) in semen can cause lipid peroxidation and damage sperm through oxidative stress, while antioxidants in semen can attenuate this damage and provide protection. Based on this principle, oral antioxidants can reduce oxidative stress damage and improve male fertility in clinical practice [7–9]. Common antioxidants include L-carnitine (LC) and N-Acetylcysteine (NAC), which can improve the damage caused by excessive oxidative stress to sperm and participate in the process of spermatogenesis [10].

L-carnitine in the human body increases sperm energy and improves sperm motility during the process of epididymis sperm transport, and also has a certain antioxidant capacity [11, 12]. Spermatogenesis is closely related to energy metabolism [13, 14]. Part of IMI may be caused by a L-carnitine deficiency, which leads to a disturbance of energy metabolism in sperm cells, further linking defects in spermatogenesis [15].

At present, LC and NAC are recommended as nutritional additives for the clinical treatment of idiopathic male infertility [16, 17], but the specific therapeutic effects have not been confirmed.

Our meta-analysis synthesized randomized controlled trials (RCTs) over the past two decades and compared the experimental group population using LC or NAC drugs with the control group population using placebo to evaluate the efficacy of these two drugs.

2. Methods

2.1 Information sources and search strategy

We performed a systematic search of RCTs in the following databases: MEDLINE (01 January 1990–01 May 2024), EMBASE (01 January 1990–01 May 2024), and the Cochrane Controlled Trials Register (01 January 1990–01 May 2024). This systematic review has been registered in PROSPERO (ID: CRD42024552120). The complete checklist file has been added in the **Supplementary material**. The search terms were as follows: "L-carnitine", "N-Acetylcysteine", "idiopathic infertile", "antioxidant" and "randomized controlled trials". We further scanned the conference abstracts and proceedings in English language for candidate articles. Besides, we looked for the list of references of the included studies as well. This meta-analysis strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) list [18]. Three authors participated independently in the literature search. Any disagreements about the screening results were discussed by two supervisors, and the final decision was based strictly on the inclusion and exclusion criteria.

2.2 Inclusion criteria, exclusion criteria and trial selection

The primary including criteria are as follows: (1) Inclusion were patients with IMI that had no identifiable medical condition that could explain infertility; (2) Comparison of LC and NAC monotherapy in men with IMI; (3) The type of study was RCT. The excluding criteria are as follows: (1) Other treatments; (2) Patients with genitourinary bacterial infections, hypogonadism, varicocele and other comorbidities; (3) Non-randomized controlled trials: editorials, reviews, commentaries, case reports, case series and single arm studies were excluded.

2.3 Quality assessment

The Cochrane manual was used to assess the quality of all included studies [19]. The quality of these individual studies was determined by their evaluation methods, including patient allocation, concealment of allocation, and blinding. Each included study was evaluated by using the guidelines published in the Cochrane Intervention System Evaluation Manual, Version 5.1.0 [19]. Each study is evaluated and classified as "+" (meeting all quality standards, with low risk of bias), "?" according to its quality (It is not clear about one or more quality standards, with a moderate risk of bias) or "−" (it barely meets the quality standards, with a high risk of bias). The differences in this classification were resolved through discussions among researchers. Table 1 (Ref. [20–26]) contains the details of the inclusion criteria.

2.4 Data extraction

We collected useful data from all relevant articles, including the name of the first author, study characteristics; study design and sample size; interventions between groups; and evaluation metrics such as sperm concentration, ejaculate volume, sperm motility, normal morphology, testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin (PRL). All authors checked the accuracy of the data.

2.5 Statistical analysis and meta-analysis

The data of this study were statistically analyzed by using the review manager software (version 5.4.0; Cochrane Collaboration, London, UK) [7]. Continuous data were analyzed with mean difference (MD), and dichotomous data were evaluated by odds ratio (OR) with 95% confidence interval (95% CI). Heterogeneity analysis: an individual study could be characterized as a fixed model if $p > 0.05$, otherwise a random-effects model was chosen for it. Statistical analysis: if $p < 0.05$, the result is considered to be statistically significant.

TABLE 1. The details of the individual studies.

Study	Country	Study design	Treatment		Sample size		Follow up	Dose	Mode of administration	Inclusion criteria
			Experiment	Control	Experiment	Control				
Safarinejad *et al*. [20]	Iran	RCT	NAC	Placebo	105	106	26 weeks	600 mg/day	Oral	Sperm count of greater than 5×10^6/mL, no factors in their history with a possible influence for male infertility, >2 years of failed attempts at conception and no female factors.
Balercia *et al*. [21]	Italy	RCT	LC	Placebo	15	15	3 months	3 g/day	Oral	Sixty infertile men, ages 20–40 years, with the following baseline sperm selection criteria: concentration $<20 \times 10^6$/mL, sperm forward motility 50%, and normal sperm morphology 30%.
Ciftci *et al*. [22]	Turkey	RCT	NAC	Placebo	60	60	3 months	600 mg/day	Oral	The patients with idiopathic infertility with normal sperm parameters were included in the present study.
Jannatifar *et al*. [23]	Iran	RCT	NAC	Placebo	50	50	3 months	600 mg/day	Oral	The infertile couples with no previous report of pregnancy, normal female partner and male partner defined as having Asthenoteratozoospermia based on WHO criteria.
Ma L *et al*. [24]	China	RCT	LC	Placebo	73	70	3 months	3 g/day	Oral	1. Adult males between 20–40 years of age with infertility for >1 year having regular sexual; 2. Normal rheological characteristics of semen with normal volume and pH; 3. No female component in infertility.
Mehni *et al*. [25]	Iran	RCT	LC	Placebo	51	59	3 months	1 g/day	Oral	Men were infertile with IMI, 25–40 years old.
Moradi *et al*. [26]	Iran	RCT	LC	Placebo	20	32	3 months	2.5 g/day	Oral	A history of infertility for at least one year; semen parameter abnormalities, including sperm concentration 6 or count $<20 \times 10^6$/mL, motility <50% with grade "a + b" or 25% with grade "a", and morphology <50%.

Note. LC: L-carnitine; NAC: N-Acetylcysteine; RCT: Randomized controlled trials; pH: Pouvoir Hydrogène; IMI: idiopathic male infertility; WHO: World Health Organization.

3. Results

3.1 Characteristics of the individual studies

Our search strategy generated 159 articles. After browsing the abstract and title, 132 articles were deleted because their content did not match the required criteria. Among the remaining 27 articles, 8 were excluded because the experimental method is not random controlled trials. 12 were excluded due to the lack of complete and useful data. Finally, our study included 7 different RCTs [20–26]. The details of the research selection process were shown in Fig. 1, and the features and characteristics of the 7 RCTs were shown in Table 2 (Ref. [21–26]).

3.2 Quality assessment of the individual studies

All included articles were RCTs. Each study introduced the treatment scheme and calculated the sample size (Table 2). The risk of bias graph is presented in Fig. 2 (Ref. [20–26]).

3.3 Sperm concentration

LC Versus Placebo. Four RCTs including 335 patients were included in the analysis. Forest plots drew an MD of 8.49 and 95% CI [7.84, 9.13] ($p < 0.001$) (Fig. 3, Ref. [20–26]). Therefore, LC had a better effect in raising sperm concentration compared with the placebo.

NAC Versus Placebo. Three RCTs including 431 patients were included in the analysis. Forest plots drew an MD of 4.17 and 95% CI [3.43, 4.91] ($p < 0.001$) (Fig. 3). Therefore, NAC could bring a significant increase in sperm concentration compared with the placebo.

3.4 Sperm motility (%)

LC Versus Placebo. Four RCTs including 335 patients were included in the analysis. Forest plots drew an MD of 11.62 mL and 95% CI [1.33, 21.91] ($p = 0.03$) (Fig. 4, Ref. [20–26]). Therefore, LC had a better effect in raising sperm motility compared with the placebo.

NAC Versus Placebo. Three RCTs including 431 patients were included in the analysis. Forest plots drew an MD of 8.44 mL and 95% CI [2.67, 14.21] ($p = 0.004$) (Fig. 4). Therefore, NAC had a significantly greater increase in sperm motility compared with the placebo.

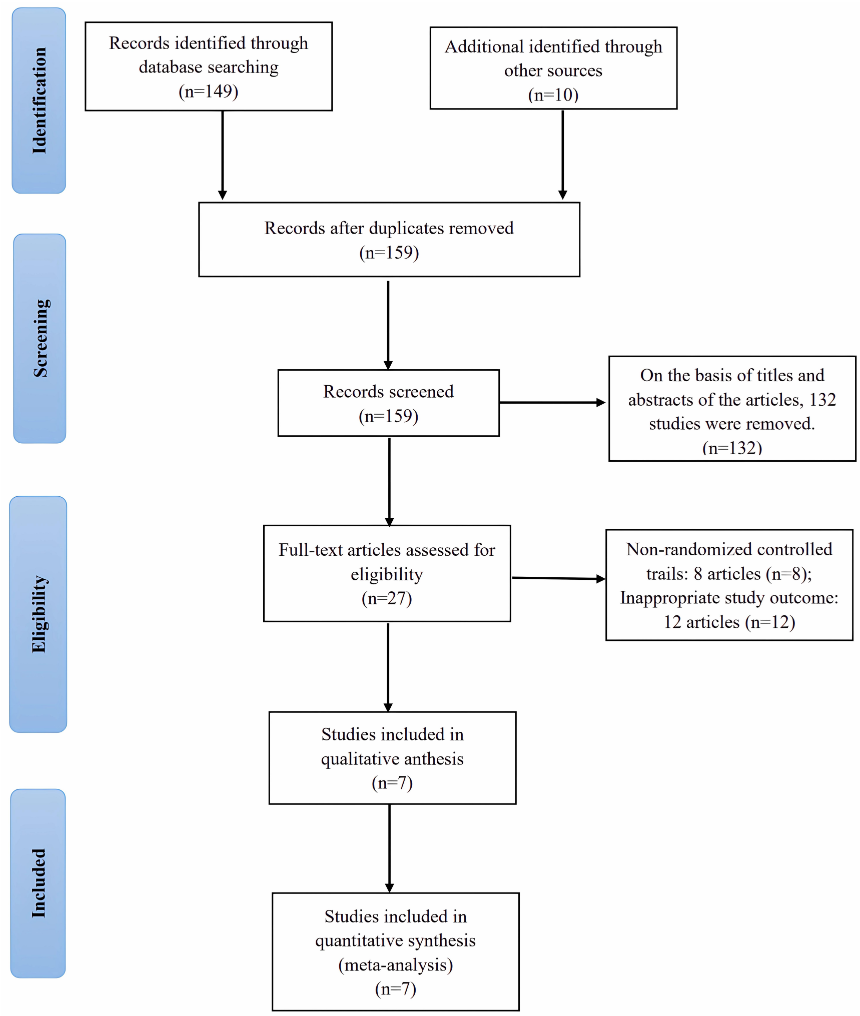

FIGURE 1. Flowchart of selection PRISMA. Note. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 2. The quality assessment of each study.

Study	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and personnel (Performance Bias)	Blinding of Outcome	Assessment (Detection Bias)	Incomplete Outcome Date (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias	Calculation of Sample Size	Statistical Analysis
Ma *et al*. [24] (2022)	+	+	+	+	+	+	+	+	Yes	Shapiro-Wilk test; student's *t*-test
Balercia *et al*. [21] (2005)	+	+	+	+	+	+	+	+	No	ANCOVA; χ^2 test
Mehni *et al*. [25] (2014)	+	+	+	+	+	+	+	+	No	ANCOVA; *t*-test
Moradi *et al*. [26] (2010)	+	+	+	+	+	+	+	+	Yes	*t*-test
Ciftci *et al*. [22] (2009)	+	+	+	+	+	+	+	+	No	Student's *t*-test
Jannatifar *et al*. [23] (2019)	+	+	+	+	+	+	+	+	No	*t*-test
Safarinejad & Safarinejad (2009)	+	+	+	+	+	+	+	+	Yes	ANOVA; Mann-Whitney U test

Note. ANCOVA: Multivariate Analysis of Covariance. ANOVA: Analysis of Variance.

FIGURE 2. Quality assessment of each study.

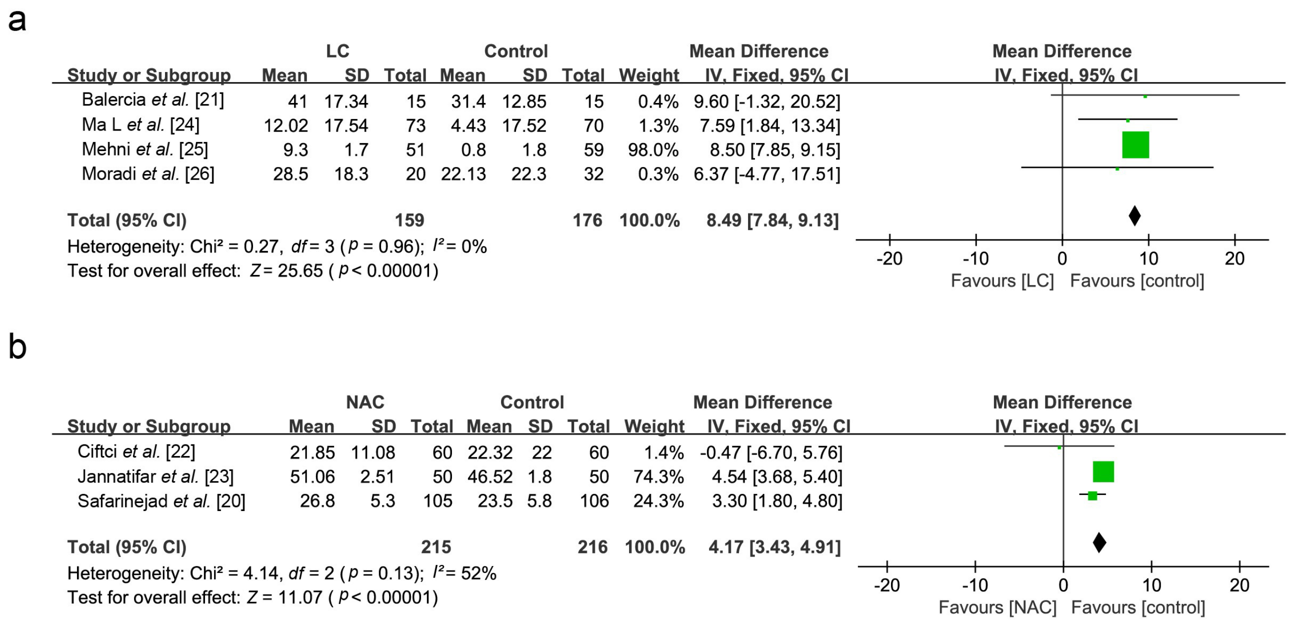

FIGURE 3. Forest plots showing results in sperm parameters on the sperm concentration. Note. (a) LC *vs.* Placebo, (b) NAC *vs.* Placebo. LC: L-carnitine; SD: standard deviation; IV: inverse variance; CI: confidence interval; *df*: degrees of freedom; NAC: N-Acetylcysteine.

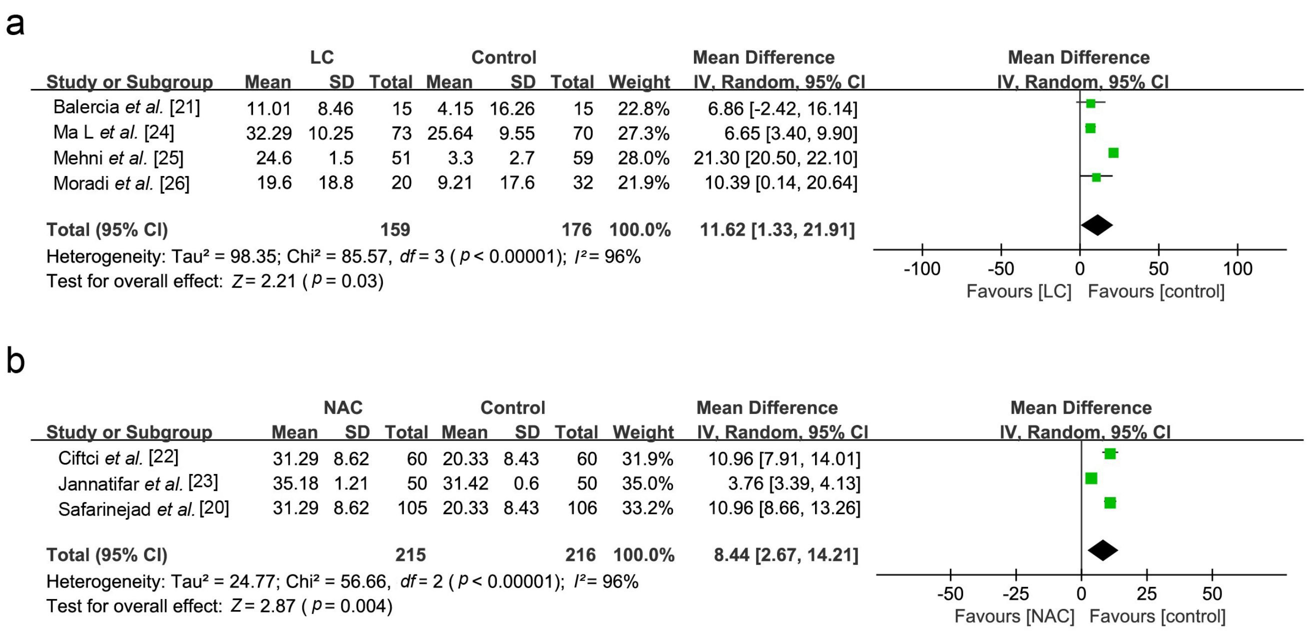

FIGURE 4. Forest plots showing results in sperm parameters on the sperm volume. Note. (a) LC *vs.* Placebo, (b) NAC *vs.* Placebo. SD: standard deviation; IV: inverse variance; CI: confidence interval; *df*: degrees of freedom; LC: L-carnitine; NAC: N-Acetylcysteine.

3.5 Normal morphology (%)

LC Versus Placebo. Four RCTs including 305 patients were included in the analysis. Forest plots drew an MD of 0.97 and 95% CI [0.14, 1.80] ($p = 0.02$) (Fig. 5, Ref. [20, 22–26]). Therefore, LC/LAC (acetyl-L-carnitine) had a better effect in raising sperm normal morphology compared with the placebo.

NAC Versus Placebo. Three RCTs including 431 patients were included in the analysis. Forest plots drew an MD of 1.68 and 95% CI [0.79, 2.58] ($p < 0.001$) (Fig. 5). Therefore, NAC had a significantly greater increase in sperm normal morphology compared with the placebo.

3.6 Sperm volume

LC Versus Placebo. Two RCTs including 82 patients were included in the analysis. Forest plots drew an MD of 0.26 and 95% CI [−1.55, 2.06] ($p = 0.78$) (Fig. 6, Ref. [20–23, 26]). Therefore, LC did not have a better effect in raising sperm volume compared with the placebo.

NAC Versus Placebo. Three RCTs including 431 patients were included in the analysis. Forest plots drew an MD of 0.69 and 95% CI [0.26, 1.12] ($p = 0.002$) (Fig. 6). Therefore, NAC could bring a significant increase in sperm volume for infertile men compared with the placebo.

3.7 Hormonal analysis

Three RCTs including 454 patients were used to estimate the level of testosterone, LH, FSH and PRL. The random model showed that there were no significant differences between antioxidant and placebo in raising the level of testosterone (MD, 0.50 ng/mL; 95% CI [0.44, 0.57]; $p < 0.001$; Fig. 7, Ref. [20, 23, 24]), LH (MD, 0.80 mIU/mL; 95% CI [−0.48, 2.08]; $p = 0.22$; Fig. 7), PRL (MD, −0.21 ng/mL; 95% CI [−0.80, 0.38]; $p = 0.49$; Fig. 7), and FSH (MD, 0.29 mIU/mL; 95% CI [−1.41, 2.00]; $p = 0.74$; Fig. 7).

4. Discussion

Varicocele, infections of the reproductive system, poor lifestyle, congenital hypoplasia of the reproductive system, contamination with heavy metal elements, and many other factors can affect the total viability and survival of the spermatozoa, which can lead to the development of IMI [1, 27]. IMI is characterized by low and weak semen indicators with no identifiable cause. At present, there is no definitive treatment for IMI, and most Western medicine is based on experiential medication [2, 28].

We respectively compared the efficacy of LC (1–3 g/day), and NAC (600 mg/day) with placebo in IMI patients 3 months after treatment. We found that two drugs can effectively increase sperm concentration, increase the proportion of sperm motility and normal sperm morphology, and NAC can also simultaneously increase sperm quantity. These data suggest that two antioxidant drugs as monotherapy can significantly improve a range of semen indicators and provide a therapeutic effect.

L-carnitine has always belonged to the third category in the International Society of Sports Nutrition dietary supplement classification and has been widely known as a weight loss or exercise supplement in recent years [29]. L-carnitine in the male epididymis exists in the form of free L-carnitine and acetyl-L-carnitine. The carnitine content in epididymal fluid gradually increases from the head to the tail of the epididymis. By working together with various substances secreted by the epididymis, it reduces sperm apoptosis, promotes sperm maturation, and enables fertilization [11, 30]. Studies have shown that the content and concentration of L-carnitine in the seminal plasma of male infertility patients are lower than those in the

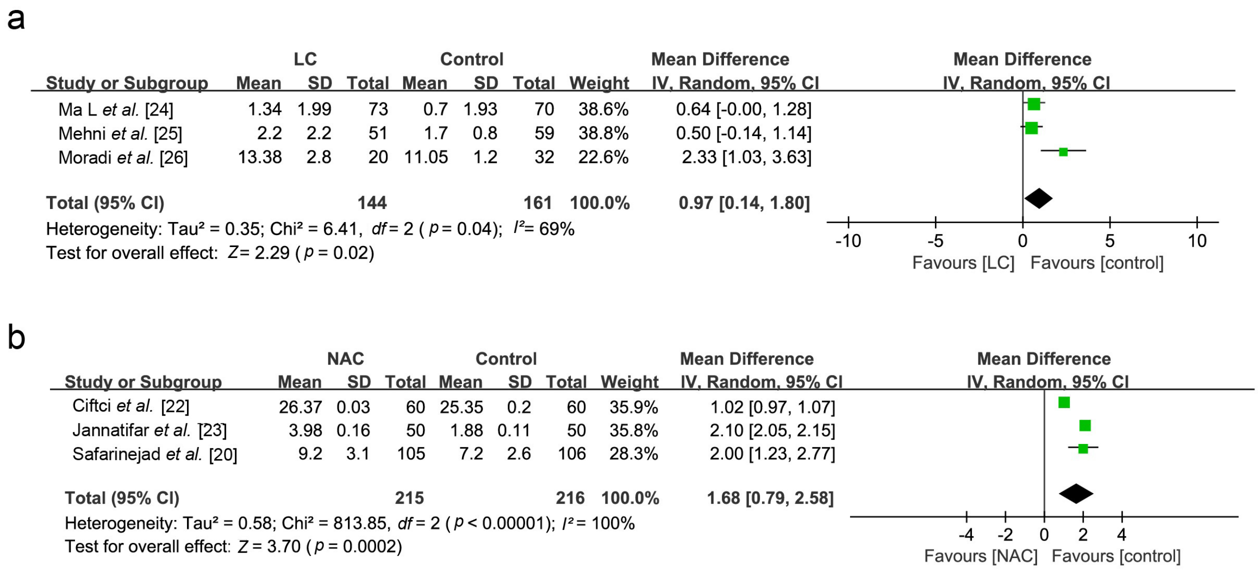

FIGURE 5. Forest plots showing results in sperm parameters on sperm motility. Note. (a) LC *vs.* Placebo, (b) NAC *vs.* Placebo. SD: standard deviation; IV: inverse variance; CI: confidence interval; *df*: degrees of freedom; LC: L-carnitine; NAC: N-Acetylcysteine.

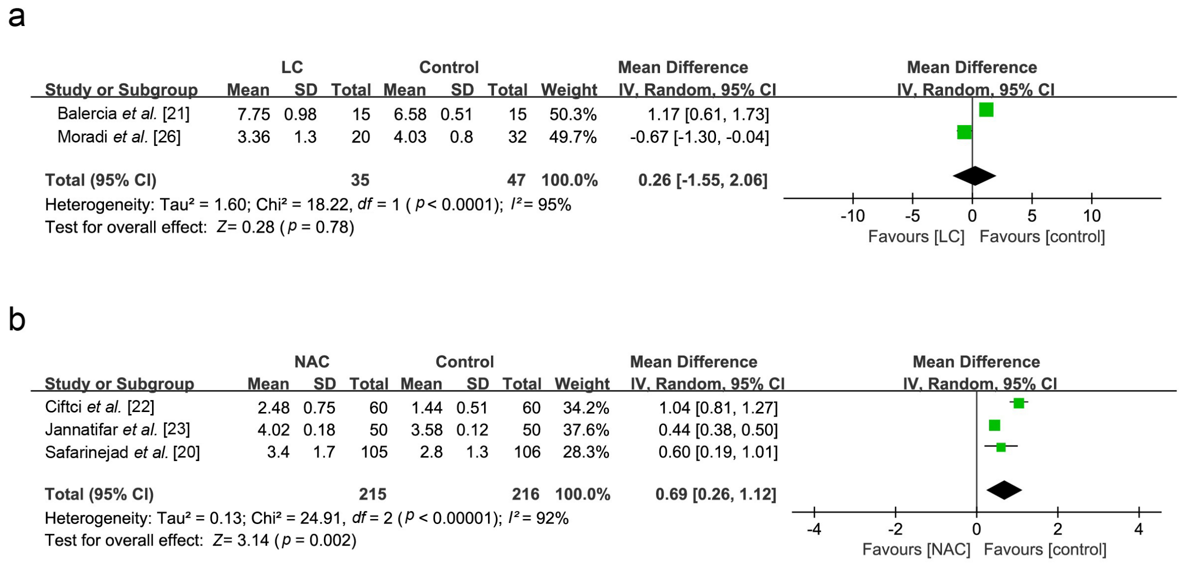

FIGURE 6. Forest plots showing results in sperm parameters on the normal morphology. Note. (a) LC *vs.* Placebo, (b) NAC *vs.* Placebo. SD: standard deviation; IV: inverse variance; CI: confidence interval; *df*: degrees of freedom; LC: L-carnitine; NAC: N-Acetylcysteine.

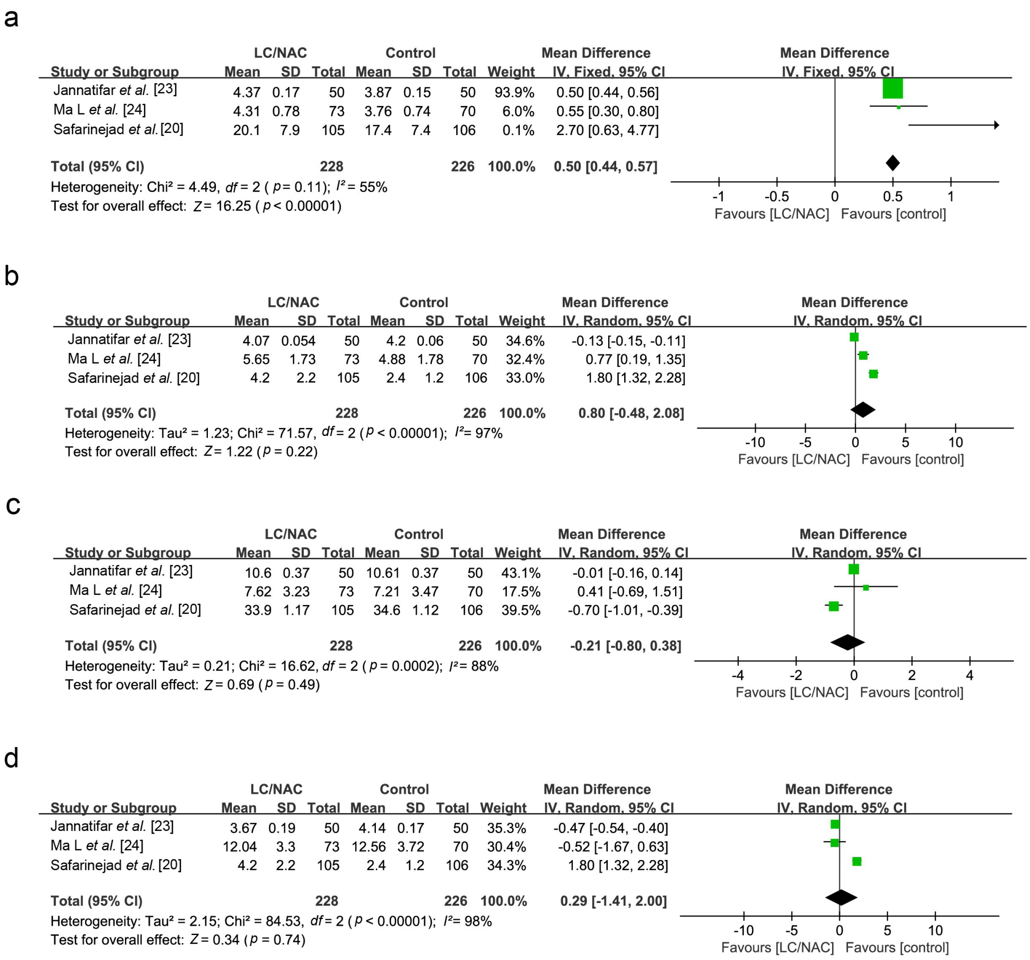

FIGURE 7. Forest plots showing results in hormonal analysis. Note. (a) Testosterone, (b) LH, (c) PRL, (d) FSH. LC: L-carnitine; SD: standard deviation; IV: inverse variance; CI: confidence interval; *df*: degrees of freedom.

normal population. The concentration of L-carnitine in semen is significantly positively correlated with sperm concentration, total sperm count, motility sperm motility, and linear movement amplitude [31–33].

In addition, L-carnitine is an important antioxidant. More and more studies have shown that when the production and removal of ROS lose their dynamic balance and are in an oxidative stress state, excessive ROS can damage the integrity of sperm cell nucleus deoxyribonucleic acid (DNA), affect the normal energy transmission of mitochondria, cause damage to sperm membrane structure, and reduce or lose sperm motility and vigor, accelerating sperm cell apoptosis [4, 34, 35]. L-carnitine can rebalance the oxidative and antioxidant status in the epididymis by improving its microcirculation, avoiding oxidative damage to sperm caused by ROS in the epididymis and semen [36]. Our study found that oral supplementation with L-carnitine could bring improvement in relevant indexes, confirming its efficacy for IMI patients.

NAC converts to L-carnitine upon ingestion, which is further converted to glutathione, scavenging free radicals and reducing oxidative stress [36]. NAC can also directly confront free radicals through the sulfur groups in its chemical composition [37]. Studies have also found that NAC can act as an inhibitor of neutrophil infiltration or protect tissues by balancing oxidative antioxidant states by preventing endoplasmic reticulum (ER) stress [38, 39].

Therefore, it has been recommended as a powerful antioxidant compound for the treatment of cardiovascular, kidney, liver, and reproductive system diseases [39]. Yu Wei *et al.* [40] found that NAC, as an exogenous antioxidant, can reduce oxidative damage to sperm DNA, maintain a balance of oxidative and antioxidant properties in the epididymis, significantly improve sperm function parameters in mice, and promote spermatogenesis. Our results also confirm that NAC can optimize the conventional and functional parameters of sperm in seminal plasma: increasing sperm volume, increasing sperm concentration, improving sperm motility and the proportion of normal sperm morphology, and recommending it for the treatment of IMI.

While analyzing changes in semen indicators, we analyzed the effects of the application of two drugs on serum hormone levels. Any changes in hormone distribution can profoundly affect chromosome ploidy and sperm chromatin integrity [20]. There are FSH receptors and testosterone receptors on supporting cells. Hormones in the blood can affect spermatogenesis by binding to receptors. Testosterone affects the successful completion of mitosis and meiosis in normal spermatogonia. In the absence of testosterone, round sperm will be lost between 7–8 steps of spermatogenesis. FSH can promote sperm production by increasing the number of supporting cells; LH can promote the development of testicular interstitial cells, and participate in testicular development and sperm production; Although the targets of PRL and its receptors in spermatogenesis are not yet clear, it has been found that their role in promoting spermatogenesis is indispensable [41–43]. Our analysis showed that there was no significant difference in serum LH, FSH and PRL levels, while both drugs could increase serum testosterone concentration. Two drugs could mainly improve testicular spermatogenic function by increasing testosterone concentration.

Through the analysis of relevant indicators, we found that these two drugs mainly exert their effects by regulating energy metabolism processes and avoiding oxidative stress. For IMI, the application of antioxidant drugs is still an important method of treatment, including commonly used health products such as vitamin E and coenzyme, and drugs such as L-carnitine and NAC. Our meta-analysis synthesized the RCTs in the past two decades. Comparing the experimental group population using LC or NAC drugs with the control group population using placebo, we found that the application of the drugs can improve the sperm quality of patients, solve the adverse indicators of IMI, and do not bring changes in serum PRL, FSH and other hormones, confirmed the efficacy and safety of the two drugs. This also suggested that a large number of IMI patients are due to the impairment of energy metabolism and the damage to sperm caused by oxidative stress. It is hoped that the prevention and treatment plan can be proposed for the current situation of high incidence of IMI. It is worth noting that the dosage range of LC used in the study is mostly 1–3 g/day, and the dosage range of NAC is 600 mg/day. Patients' relevant indicators are mostly analyzed after 3 months of treatment. Due to the dependence of ROS clearance on drug dosage, it is necessary to maintain ROS at a normal level. The antioxidants can serve as both savior and stressor, so the therapeutic effect is highly sensitive to drug dosage, and the application of such drugs needs to be within a strict dose range [44].

Acetyl L-carnitine (ALC) is an acetylated product of L-carnitine and is also the most abundant derivative of L-carnitine that naturally exists in living organisms. Many clinical trial results recommend that the combination of L-carnitine and acetyl-L-carnitine is a breakthrough in the field of male infertility drug treatment in recent years [32]. Guangzhou Wei *et al.* [45] conducted a meta-analysis in 2021 and found that the combined use of LC/LAC or NAC can significantly improve sperm motility and normal morphology. Our study focused on the efficacy of LC monotherapy. The experimental group only used LC monotherapy and found that LC monotherapy can also effectively improve sperm motility, and sperm concentration, and increase the proportion of normal sperm morphology. Compared with the combined use of two drugs, this not only brings good therapeutic effects, but also reduces the burden of medication on patients, improves their compliance, and reduces the occurrence of toxic and side effects of drug use. Therefore, the monotherapy of LC also deserves attention.

Selection bias and subjective bias can affect the final results, our independent screening of the literature by multiple authors reduced this bias. However, our analysis still had limitations and shortcomings. The number of included studies was limited, and the underlying metrics of the RCTs were not entirely consistent. Further studies are still needed.

5. Conclusion

LC and NAC are two commonly used antioxidant drugs for patients with IMI. Both can improve sperm motility, increase sperm concentration and the proportion of normal sperm morphology. NAC can also increase the concentration of serum testosterone. Both monotherapies can bring good therapeutic effects on IMI.

AVAILABILITY OF DATA AND MATERIALS

All data was contained within this article.

AUTHOR CONTRIBUTIONS

YSC and JTW—designed the research study. XHM—performed the research. YYY—provided help and advice on the statistical methods. SGL—analyzed the data. XHM, YYY and SGL—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://files.intandro.com/files/article/1905178128489037824/attachment/Supplementary%20material.docx.

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