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A comparative study between N-acetylcysteine and L-carnitine in the management of male infertility (placebo-controlled trial)

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Abstract. ***Background.*** *Male infertility is a globally recognised health condition, which is mainly reported in the age range of 35–39 years. Males from at least three in six couples are impacted by infertility on a global scale. Research evidence reveals the therapeutic benefits of L-carnitine and N-acetylcysteine for infertile males; however, the current evidence is limited by high heterogeneity in contemporary studies. Therefore, this study aimed to investigate the influence of these treatments on sperm parameters and the semen's malondialdehyde level and total antioxidant capacity.* ***Materials and methods.*** *This randomised placebo-controlled clinical trial deployed 180 male patients with normal female factor and idiopathic oligoasthenoteratozoospermia from January 2021 to December 2024. The patients in the age group of 25–40 years were randomised into L-carnitine (1000 mg oral dose), N-acetylcysteine (oral dose), and placebo (sugar sachets) treatments. The baseline data included the patient's age and sperm parameters (including sperm motility, sperm concentration, sperm morphology, and semen volume). The semen parameters in the study groups were re-investigated after six months of the study intervention. Additionally, total antioxidant capacity and malondialdehyde levels in the semen were evaluated before and after the treatment administration.* ***Results.*** *The six-monthly analysis revealed that the sperm parameters, including sperm motility (38 and 38 vs. 4 %), morphology (30 vs. 29 vs. 7 %), and concentration (25 and 24 vs. 2 %), significantly improved with the administration of N-acetylcysteine and L-carnitine, respectively, in comparison to the placebo. However, semen volume (6 and 5 vs. 4 %) was not impacted by either treatment and did not differ significantly from the placebo group ($p > 0.05$). Compared to pretreatment, N-acetylcysteine monotherapy improved the total antioxidant capacity (1.92 ± 0.12 vs. 2.61 ± 0.12; $p = 0.01$) and reduced the level of malondialdehyde (2.46 ± 0.11 vs. 1.85 ± 0.10; $p = 0.01$) in the semen. However, in comparison to the placebo, these improvements were not observed with L-carnitine monotherapy.* ***Conclusions.*** *The oral L-carnitine and N-acetylcysteine treatments effectively improved sperm concentration, morphology, and motility in male patients with infertility. However, as a single-agent therapy, no statistically significant differences were observed between the outcomes of N-acetylcysteine and L-carnitine. In addition, N-acetylcysteine appeared superior to L-carnitine in reducing the oxidative stress and malondialdehyde levels in the seminal plasma. Prospective studies should identify the mechanisms underlying the efficacy of L-carnitine/N-acetylcysteine and evaluate the safety and effectiveness of combination antioxidant treatments against male infertility.*

Keywords: *male infertility; N-acetylcysteine; L-carnitine; motility; morphology; total antioxidant capacity; malondialdehyde; sperm; semen*

Introduction

Male infertility is globally reported in at least three in six couples and is predominantly impacted by societal and cultural attributes [1, 2]. Nearly 3×10^5 disability-adjusted life years were observed in 55 million infertile males across the world in 2021 [1]. Male infertility is mainly reported in the age range of 25–40 years [1, 3]. While a significant increase in age-standardised rates of male infertility is specifically reported in Eastern Europe, high-severity cases are observed in Eastern European and African regions. Male infertility

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increases the risk of deterioration in psychological well-being, reduction in family/community integrity, and an overall decline in population health [4]. The prevalence of male infertility reciprocates with sociodemographic index, age, and location. The regions such as Southeast Asia, South Asia, and Saharan Africa with reduced sociodemographic index have an elevated burden of male infertility [1, 3]. The past three decades have witnessed an unprecedented increase in the worldwide occurrences of male infertility due to insufficient assisted reproductive interventions, unhealthy lifestyles, sexually transmitted diseases, and health-inappropriate environments [5]. The psychosocial outcomes of male infertility include selective sharing of infertility diagnosis, relationship crises, emotional turbulence, and changes in perspectives toward society [6].

A decline in male reproductive health is indicated by low semen quality [3]. The abnormal semen attributes include the increased time of sperm liquefaction, reduced volume of ejaculation, low motility of the sperm, and decline in semen count and motility. However, the sperm of the infertile males may still appear normal in morphology. It is important to note that the aetiology of > 30 % of male infertility cases is not yet determined [7, 8]. Furthermore, nearly 30 % of males with infertility are impacted by idiopathic oligoasthenoteratozoospermia (iOAT) [9]. The predominant causes of iOAT include hormonal changes, environmental effluents, and mutations in the mitochondrial DNA and the genome of the gamete [10]. The morphology, motility, and concentration of the sperm in infertile males are predominantly impacted by apoptosis and in scenarios when the seminal plasma and tubules are overburdened with reactive oxygen species [8]. Infertile males with iOAT are affected with less than 4 % of normal sperm (teratozoospermia), less than 32 % of progressively motile sperm (asthenozoospermia), and less than 15 million/ml sperm concentration (oligozoospermia) [7].

Additionally, male infertility is associated with reduced sperm function under the influence of oxidative stress [11]. The sperm of infertile men lose their motility and fluidity due to the deterioration of their membrane via lipid peroxidation. The deterioration of offspring outcomes and infertility are also triggered by a significant decline in the genetic integrity of the sperm due to its DNA fragmentation via reactive oxygen species [12]. The impacted sperm fails to fertilise the egg due to low motility and disfigurement of its structured proteins, caused by protein oxidation. Pollution and smoking (environmental factors), dysfunction of the mitochondria, and activity of the leukocyte are the potential causes of the sperm's oxidative stress in infertile males [13]. Of note, since the repair processes in the spermatozoa are limited, it is prone to deterioration in spite of the antioxidant defences in the body [14]. This is why lifestyle modification and antioxidant therapies are highly recommended to subdue the adverse impact of oxidative stress on the function of the sperm. The natural antioxidants with the ability to counter oxidative stress in the sperm include copper, selenium, zinc (micronutrients), carnitine, coenzyme Q10, pantothenic acid, glutathione, vitamin B complex, vitamin C, vitamin E, and vitamin A [15]. In asthenozoospermic men, the administration of oral antioxidants helps minimise oxidative damage by neutralising the reactive oxygen species [16]. They also normalise the seminal plasma's oxidation-reduction potential, reverse leukocytospermia, and minimise the DNA fragmentation in the sperm [17, 18].

The antioxidant potential of the glutathione and cysteine precursor, N-acetylcysteine, is due to its ability to facilitate antioxidant signalling, replenishment of glutathione, and scavenging of oxidants [19]. The orally administered N-acetylcysteine (11 g admixed with H_2O (300 ml)) reaches its maximum plasma concentration (27 μg/ml) in two hours. N-acetylcysteine has a protein binding capacity of 66–87 % and a steady state distribution volume of 0.47 L/kg [20]. This drug has the ability to form conjugates, disulfide, and cysteine [20]. The mean clearance and mean half-life of N-acetylcysteine are 0.11 L/hour/kg and 7 hours, respectively [20]. Research evidence from a meta-analysis reveals that in idiopathic infertile males, the morphology of the sperm, sperm motility, ejaculate volume, and concentration of the sperm can be enhanced with the daily administration of oral N-acetylcysteine [21]. Another piece of evidence from a randomised-controlled study states that orally administered N-acetylcysteine resulted in a noticeable post-treatment decline in protamine deficiency, DNA fragmentation, abnormal sperm morphology, and a marked elevation in sperm motility and sperm count [22].

Similarly, the antioxidant L-carnitine is known for its ability to act on the inside of the mitochondrial membrane and facilitate long-chain fatty acid transport [23]. It also supports recovery in athletes after exercise and helps to enhance their performance. Research has revealed the possible role of L-carnitine in improving testicular function by minimising the concentration of reactive oxygen species [24]. Findings from a recent retrospective analysis revealed the potential of oral L-carnitine (2000 mg) in improving embryo quality and sperm attributes. L-carnitine also helps to treat asthenoteratozoospermia, which may minimise the use of assisted reproduction technology [25]. A recent case study analysed the outcomes of asthenozoospermic patients after modifying their lifestyles, adding antioxidants to their diets, and administering oral L-carnitine (3000 mg) per day for a month's duration [26]. The posttreatment assessment indicated a 3–7 % improvement in normal sperm morphology, elevation in sperm count (from 25 to 49 million/ml), and a significant enhancement in sperm motility (from 15 to 50 %) [26]. These results restated the possible role of L-carnitine in improving fertility parameters, oxidative stress, and the function of mitochondria in the sperm.

The contemporary studies have not acquired any consensus on the comparative evidence concerning the efficacy of N-acetylcysteine and L-carnitine against male infertility. A meta-analysis of studies focusing on idiopathic asthenozoospermia indicated a significant elevation in the volume of the ejaculate and concentration of the sperm in infertile males who were treated with N-acetylcysteine [27]. In addition, L-carnitine treatment enhanced the volume of the ejaculate and the concentration of the sperm. Contrarily,

another umbrella analysis of clinical trials and real-world studies revealed that N-acetylcysteine lacks the potential to enhance the rates of pregnancy and sperm count and can only increase the concentration of sperm cells with normal shape along with their swimming patterns [28]. A recent meta-analysis revealed yet another contradictory evidence regarding the role of both N-acetylcysteine and L-carnitine in improving pregnancy outcomes as well as morphology, motility, and concentration of the sperm (i.e., all sperm attributes) in idiopathic infertile males [29]. These gaps in the highly heterogeneous contemporary evidence warrant the organisation of randomised controlled studies to investigate the clinical effectiveness of L-carnitine and N-acetylcysteine in infertile adult men. Accordingly, this study aimed to evaluate the efficacy and outcomes of orally administered N-acetylcysteine and L-carnitine in young adult males with a definitive diagnosis of infertility.

Materials and methods

Participants

This randomised placebo-controlled clinical trial began in January 2021 and continued till December 2024 in the Saladin province of Iraq. One hundred eighty male participants with a laboratory-confirmed diagnosis of infertility were recruited in this study. The patients were randomised into three equal groups (n = 60 each). The first group of patients (n = 60) received a 1000 mg oral dose of L-carnitine. The second group was treated with N-acetylcysteine; however, sugar sachets (or placebo treatment) were administered to the third group. Each of the study groups received their respective treatments exclusively for a duration of six months.

Inclusion and exclusion criteria

Adults aged 25–40 years with normal female factor and iOAT were included in this study. Alternatively, those with obstructive azoospermia, varicocele, scrotal tumours, genital trauma, or genital infection were excluded from this analysis. Notably, patients below 25 years and above 40 years of age were also excluded from this clinical trial.

Data collection and statistical analysis

At the start of the study (or day 0), the baseline data were collected after analysing the semen samples from all participants. Age, marriage time, job type, and habits were additionally recorded from each patient through interactive interviews. Following the initial six months of the study treatments, the semen samples were recollected for subsequent assessment. The laboratory analysis of the study samples required a maximum time of 15 minutes. The WHO 2021 parameter guided the interpretation of the study samples [30]. The Kruger criteria were utilised to investigate the semen morphology [31]. The authors used Windows SPSS (version 26.0) for data analysis. The significance of the results from the chi-square, Kruskal-Wallis, and Mann-Whitney U tests was determined with the probability value reference ($p < 0.05$) [32, 33].

Ethical parameters

All study procedures and interventions were thoroughly explained to each of the study participants. The objectives and concerns regarding the study were categorically explained to the enrollees. Interactive discussions were organised to address and resolve the concerns and questions of the participants regarding the research study. All the research participants provided written informed consent for the study. The ethical approval for the study was obtained from the local Institutional Review Board.

Study procedures

A Doppler study was performed on all study participants to rule out varicocele. Pre- and post-treatment assessments of seminal plasma were undertaken through precipitation and centrifugation techniques. Malondialdehyde and total antioxidant capacity were evaluated to reveal the oxidative stress and the antioxidant defence of the semen in each participant.

Results

Table 1 depicts age, sperm motility, sperm concentration, sperm morphology, and semen volume in each of the study groups before the study treatments. The mean age of the participants was 30 years, and the percentage of normal motility (grade a + grade b) ranged from 23 to 24 %. The sperm concentration varied from 47.2 to 48.4 million/ml across the study groups. The percentage of normal morphology as per Kruger criteria ranged from 7 to 8 % between the N-acetylcysteine, L-carnitine, and placebo groups. The semen volume fluctuated from 2.4 to 2.5 ml across the participants. Notably, no statistically significant differences were observed in each of the patient domains between the study groups before the study initiation ($p > 0.05$).

Table 2 provides post-intervention data regarding the sperm parameters after six months of the study initiation.

Table 1. Patient domains before the start of the therapy

Domains	N-acetylcysteine (n = 60)	L-carnitine (n = 60)	Placebo group (n = 60)	P value
Age (years)	30.2 ± 9.2	30.1 ± 9.6	30.2 ± 8.6	> 0.05
% of normal motility (grade a + b)	23	24	23	> 0.05
Sperm concentration (million/ml)	48.4 ± 12.3	47.2 ± 10.1	47.5 ± 8.2	> 0.05
% of normal morphology (Kruger criteria)	7	8	8	> 0.05
Semen volume (ml)	2.54 ± 1.23	2.51 ± 0.85	2.42 ± 0.92	> 0.05

Compared to the placebo group, N-acetylcysteine and L-carnitine groups had statistically significant improvements in sperm motility ($p = 0.01$), morphology ($p = 0.03$), and concentration ($p = 0.01$). However, improvements in the semen volume did not significantly differ between the treatment and placebo groups ($p > 0.05$). Furthermore, the findings did not reveal statistically significant differences in outcomes between the N-acetylcysteine monotherapy and the L-carnitine monotherapy.

Table 3 and the corresponding Fig. 1 depict malondialdehyde levels and total antioxidant capacity in the semen of the study participants before and after the administration of study treatments. The results revealed a significant increase in total antioxidant capacity in patients treated with N-acetylcysteine ($p = 0.01$). They also indicated a significant decline in malondialdehyde levels after N-acetylcysteine treatment. Alternatively, L-carnitine therapy did not significantly influence the semen malondialdehyde levels and total antioxidant capacity in the respective patients ($p \geq 0.05$).

Discussion

The six-monthly analysis revealed that the sperm parameters, including sperm motility, morphology, and concentration, significantly improved with the administration of N-acetylcysteine and L-carnitine to male patients with infertility. However, semen volume was not impacted by either treatment and did not differ significantly from the placebo group. These outcomes indicate the effectiveness of N-acetylcysteine and L-carnitine monotherapies in improving the overall quality of semen in infertile males. Another noticeable finding from this study was that N-acetylcysteine monotherapy improved the total antioxidant capacity of the semen and reduced the level of malondialdehyde in the semen. However, in comparison to the placebo, these improvements were not observed with L-carnitine monotherapy.

Findings from this study support the outcomes of an umbrella assessment of the randomised controlled studies that indicated the effectiveness of orally administered N-acetylcysteine in terms of enhancing normal morphology, sperm motility, and sperm concentration [21]. However, the results contradicted the outcome, stating that

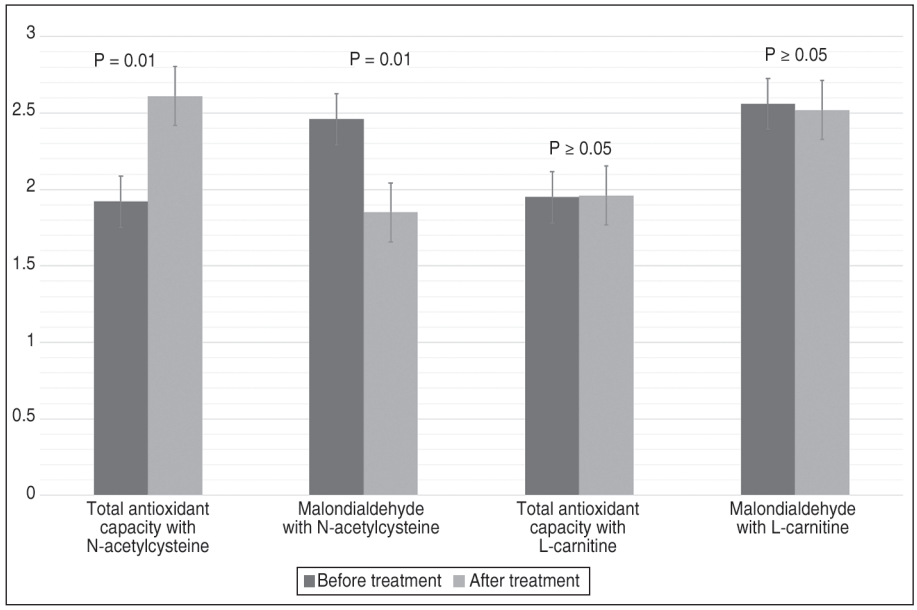

Figure 1. Malondialdehyde and total antioxidant capacity before and after treatment

Table 2. Improvements in motility, morphology, and concentration of the sperm by the end of the six months of the study, %

Domains	N-acetylcysteine (n = 60)	L-carnitine (n = 60)	Placebo group (n = 60)	P value
Motility improvement	38	38	4	0.01
Morphology improvement	30	29	7	0.03
Concentration improvement	25	24	2	0.01
Volume improvement	6	5	4	> 0.05

Table 3. The levels of malondialdehyde and total antioxidant capacity before and after treatment

Domains	Before treatment	After treatment	P value
TAC with NAC (n = 60)	1.92 ± 0.12	2.61 ± 0.12	0.01
MAD with NAC (n = 60)	2.46 ± 0.11	1.85 ± 0.10	0.01
TAC with L-carnitine (n = 60)	1.95 ± 0.12	1.96 ± 0.14	≥ 0.05
MAD with L-carnitine (n = 60)	2.56 ± 0.12	2.52 ± 0.11	≥ 0.05

N-acetylcysteine successfully improved the ejaculate volume in males with a diagnosis of infertility. A randomised clinical study by Jannatifar et al. aligned with the current findings, stating that marked improvements in sperm count and sperm motility were observed in infertile males following their treatment with N-acetylcysteine [22]. However, this study emphasised the therapeutic benefits of N-acetylcysteine for infertile males with a month's treatment duration. Another randomised study by Ciftci et al. contradicted the current finding by revealing a significant increase in semen volume in infertile males after treating them with 600 mg oral N-acetylcysteine per day. The results from this study, however, supported our outcome concerning the improvement in sperm motility with N-acetylcysteine therapy. The additional findings revealed significant improvement in semen viscosity and a decline in serum reactive oxygen species in infertile male patients who underwent N-acetylcysteine treatment. The result contradicted our finding by indicating that oral N-acetylcysteine failed to improve sperm count and sperm morphology in males with infertility. Another randomised analysis by Safarinejad et al. advocated the possible role of the combination therapy of N-acetylcysteine and selenium in enhancing the overall semen quality, indicated by improved normal morphology of the sperm, sperm motility, and mean sperm concentration [34]. However, these results did not substantiate the sperm quality improvement ability of N-acetylcysteine when administered exclusively in the absence of combination therapy. The observations from this study support the outcomes from the systematic review of 84 studies that substantiate the role of N-acetylcysteine in elevating testicular function and spermatogenesis [35]. In contrast to the current belief, an in vitro experimental study indicated the possible role of prophylactically administered N-acetylcysteine in elevating the DNA fragmentation and immature chromatin level in the sperm of males with infertility [36]. The findings from this study also revealed an elevation in cellular antioxidant glutathione and oxidative levels following the N-acetylcysteine therapy, which also altered the cytotoxic effects of etoposide and other similar chemotherapeutic agents in sperm. These results indicate the possibility of an alternative mechanism of action (other than a DNA-based mechanism) of N-acetylcysteine on the human sperm.

A contemporary prospective analysis by Nazari et al. revealed an improvement in semen quality (i.e., sperm morphology) in infertile men who were treated with L-carnitine (1500 mg)-based supplementation of antioxidants [37]. However, contrary to our findings, the antioxidant therapy did not significantly improve sperm motility. Observations from another contemporary randomised clinical trial indicated that three-monthly treatment with L-carnitine-based antioxidants improved sperm motility and reduced the DNA fragmentation index [38]. However, the results negated any influence of L-carnitine treatment on DNA decondensation in the sperm and enhancement in the sperm parameters, such as vitality, count, and volume. Furthermore, L-carnitine-oriented therapy also enhanced the live birth and clinical pregnancy rates in the participants. A meta-analysis of seven studies indicated that L-carnitine can effectively enhance sperm morphology, progressive sperm motility, and total sperm motility [28]. However, findings from this assessment denied any role of L-carnitine in improving the overall concentration of sperm in males with idiopathic infertility. These findings are supported by a review article that revealed the ability of L-carnitine to minimise oxidative damage of the sperm by the reactive oxygen species, enhance the functional and conventional sperm parameters, and safeguard the testes [39]. Another randomised-controlled study revealed a progressive decline of the sperm DNA fragmentation index with three months of treatment with L-carnitine and enhancement of sperm vitality, progressive motility, and volume with six months of therapy [40]. The authors of this study linked progressive motility of the sperm with elevated concentrations of alpha-glucosidase and seminal carnitine. They further correlated > 10 % sperm motility with a reduced DNA fragmentation index [40]. They suggested the positive role of micronutrients and metabolic attributes in improving fertility rates in male populations. Except for the literature findings concerning the semen volume improvement, our study reaffirmed the effectiveness of L-carnitine in enhancing sperm parameters.

A review paper supports our findings concerning the potential of N-acetylcysteine in improving the sperm's total antioxidant capacity, which helps to minimise oxidative damage of DNA and restore the sperm's motility [41]. A similar result was revealed by a network meta-analysis that provided evidence concerning the role of N-acetylcysteine and L-carnitine combination in reversing oxidative stress [42]. However, this finding contradicts our results that negate the improvement in total antioxidant capacity of the semen with N-acetylcysteine, while excluding the L-carnitine treatment. Of note, the authors of this study also revealed the beneficial effects of other antioxidants, such as vitamin C, vitamin E, zinc, selenium, omega-3 fatty acids, and coenzyme Q10, on sperm parameters. However, this analysis was beyond the scope of the current study. Other contemporary studies describe carnitines as potential energy sources with the capacity to neutralise free radicals in the semen [43]. Our results dispute these findings by refuting any significant influence of L-carnitine monotherapy on the semen's total antioxidant capacity.

The reduction of malondialdehyde with N-acetylcysteine in our study correlates with the plausible role of this supplement in minimising epididymal lipid peroxidation, thereby improving lipid metabolism in the testes. The possible mechanisms of this improvement include the enhancement of the level of oxidative enzymes and the NRF2 gene with oral N-acetylcysteine treatment [44]. These findings reaffirm the antioxidant capacity of N-acetylcysteine that helps to reverse the sperm's oxidative deterioration and enhance the sperm's membrane integrity, chromatin consistency, morphology, and viability [45]. The findings from this study are against the general perception of the ability of L-carnitine to reduce the malondialdehyde levels in the testes. Contemporary studies advocate the role

of L-carnitine in improving the overall activity of the antioxidant system and minimising oxidative stress responses in the testicular environment [46, 47]. Since our results do not contradict the protective effect of L-carnitine on the sperm parameters, no impact of L-carnitine monotherapy on malondialdehyde level in the current study warrants further investigation.

The oxidative stress in the testes develops with a significant decline in the antioxidant enzymes/antioxidants, which increases the risk and incidence of the deterioration of the sperm's DNA, motility, membrane integrity, and membrane fluidity [48]. The oxidative stress compromises the DNA structure and function by increasing the concentration of reactive oxygen species. L-carnitine is known to minimise sperm apoptosis, enhance mitochondrial function, protect the integrity of the plasma membrane, and improve lipid metabolism [49]. The antioxidant properties of L-carnitine and N-acetylcysteine indicate their ability to alter the oxidation mechanism based on the transport of the products of beta-oxidation toward the Krebs cycle via mitochondria. Both oral treatments possibly minimise the intracellular reactive oxygen species concentration in the testes [48]. Scientific literature depicts the role of N-acetylcysteine in improving the antioxidant potential of catalase, glutathione peroxidase, and other similar antioxidant enzymes that help to counter the rising levels of reactive oxygen species in the male reproductive environment [48, 50]. Notably, the reactive oxygen species are produced with increased mitochondrial oxidative phosphorylation. The N-acetylcysteine and L-carnitine combination controls the intracellular reactive oxygen species accumulation that eventually minimises the mitochondrial membrane potential and improves sperm motility [22]. The literature results emphasise the need to adjust and optimise the dosages of N-acetylcysteine and L-carnitine to improve sperm parameters [51]. However, to date, there is no consensus on the dosage and duration of these treatments for male patients with infertility. The possible mechanism concerning sperm motility improvement with L-carnitine and N-acetylcysteine is that the combination treatment ceases the superoxide anion reduction, reduces DNA deterioration, and enhances spermatogenesis and sperm metabolism [48].

The International Society of Sports Nutrition dietary supplement classification's third category includes L-carnitine as an antioxidant supplement [52]. The acetyl L-carnitine and L-carnitine exist in free form in the male epididymis. The maximum concentration of L-carnitine is found in the lower epididymis, and it facilitates fertilisation and maturation of the sperm. In infertile males, the seminal plasma's L-carnitine concentration and content are reduced in comparison to those of fertile males [23]. Literature provides evidence regarding a positive association between sperm concentration and L-carnitine levels [53]. Importantly, glutathione is produced from the increased accumulation of L-carnitine, which is transformed from the orally administered N-acetylcysteine. This glutathione plays a pivotal role in minimising oxidative stress by reducing the accumulation of free radicals [54]. Additionally, the sulfur group in the untransformed N-acetylcysteine effectively neutralises the free radicals, which further lowers the oxidative stress. The contemporary evidence also advocates the role of N-acetylcysteine in reducing stress in the endoplasmic reticulum and countering the infiltration of neutrophils [52]. This exogenous antioxidant utilises these mechanisms to sustain the epididymis' antioxidant properties and maintain the oxidative balance in the testes. However, the acetylated form of L-carnitine not only controls lipid peroxidation and DNA damage but also enhances the mitochondrial activity and the ATP content in the sperm [55]. The L-carnitine achieves these benefits by improving beta-oxidation in mitochondria through the increased transport of fatty acids across its inner membrane. The increased provision of energy eventually enhances the motility of the sperm. The mechanisms governing the mitochondrial activity and ATP production improvement by L-carnitine relate to the entrapment of additional acetyl-coenzyme A by acetyl-L-carnitine [52]. The deficit of acetyl-CoA helps to improve the citric acid cycle and pyruvate dehydrogenase capacity. L-carnitine uses its sodium-potassium pump and balances the energy production and homeostasis in mitochondria by facilitating the partial exclusion of sodium chloride [56]. Future studies are warranted to further understand and unravel the intricate mechanism of action of N-acetylcysteine and L-carnitine in relation to their sperm parameter/quality improvement potential.

Limitations

Despite its randomised placebo-controlled design, this study is not devoid of noticeable limitations. First, the single-centre analysis and limited sample size restrict the generalizability of outcomes across wider male populations with infertility diagnoses. Second, the limited (i.e., six months) follow-up duration and no assessment of the fertility hormones such as prolactin, follicle-stimulating hormone, luteinizing hormone, and testosterone in patients with N-acetylcysteine/L-carnitine and placebo treatments impact the reliability of outcomes. Finally, this study did not evaluate the dose-dependent outcomes and mechanism of action of N-acetylcysteine and L-carnitine, which require further assessment through prospective studies.

Conclusions

This study revealed the effectiveness of orally administered L-carnitine and N-acetylcysteine in improving sperm parameters, including sperm concentration, morphology, and motility. The findings revealed no significant statistical difference between the use of N-acetylcysteine and L-carnitine as a single-agent therapy. Compared to L-carnitine treatment, N-acetylcysteine had a significantly greater role in achieving total antioxidant capacity and lowering the seminal plasma malondialdehyde levels. Future studies should evaluate the mechanisms underlying the therapeutic effects of oral L-carnitine and oral N-acetylcysteine in infertility and reinvestigate the role of these treatments in improving semen volume.

Recommendations

The findings from this study advocate the use of L-carnitine/N-acetylcysteine monotherapy in improving sperm quality in patients with iOAT. N-acetylcysteine can be the preferred adjunctive treatment for infertility in males based on its greater potential to manage oxidative stress. Future randomised-controlled studies should aim at evaluating the role of combination antioxidant therapies in improving fertility rates across the male population.

Ethical approval

All ethical requirements and supporting documentation were fully adhered to and applied as part of the research process.

References

1. Shan Z, Chen S, Zhou W, Yang Y, Zhang G, Zhao J. Analysis of the burden of disease for male infertility globally and in China from 1990 to 2021. Transl Androl Urol. 2025 May 30;14(5):1363-1378. doi: 10.21037/tau-2025-44.

2. Leslie SW, Soon-Sutton TL, Khan MAB. Male Infertility. 2024 Feb 25. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2025 Jan.

3. Huang B, Wang Z, Kong Y, Jin M, Ma L. Global, regional and national burden of male infertility in 204 countries and territories between 1990 and 2019: an analysis of global burden of disease study. BMC Public Health. 2023 Nov 8;23(1):2195. doi: 10.1186/s12889-023-16793-3.

4. Biggs SN, Halliday J, Hammarberg K. Psychological consequences of a diagnosis of infertility in men: a systematic analysis. Asian J Androl. 2024 Jan 1;26(1):10-19. doi: 10.4103/aja202334.

5. Tesarik J. Lifestyle and Environmental Factors Affecting Male Fertility, Individual Predisposition, Prevention, and Intervention. Int J Mol Sci. 2025 Mar 20;26(6):2797. doi: 10.3390/ijms26062797.

6. De Vries CEJ, Veerman-Verweij EM, van den Hoogen A, de Man-van Ginkel JM, Ockhuijsen HDL. The psychosocial impact of male infertility on men undergoing ICSI treatment: a qualitative study. Reprod Health. 2024 Feb 19;21(1):26. doi: 10.1186/s12978-024-01749-6.

7. García-Baquero R, Fernández-Ávila CM, Álvarez-Ossorio JL. Empiric therapy for idiopathic oligoasthenoteratozoospermia. Actas Urol Esp (Engl Ed). 2020 Jun;44(5):281-288. doi: 10.1016/j.acuro.2019.10.007.

8. Cavallini G. Male idiopathic oligoasthenoteratozoospermia. Asian J Androl. 2006 Mar;8(2):143-157. doi: 10.1111/j.1745-7262.2006.00123.x.

9. Imamovic Kumalic S, Pinter B. Review of clinical trials on effects of oral antioxidants on basic semen and other parameters in idiopathic oligoasthenoteratozoospermia. Biomed Res Int. 2014;2014:426951. doi: 10.1155/2014/426951.

10. Rahimi Darehbagh R, Khalafi B, Allahveisi A, Habiby M. Effects of the Mitochondrial Genome on Germ Cell Fertility: A Review of The Literature. Int J Fertil Steril. 2022 Apr;16(2):70-75. doi: 10.22074/IJFS.2021.527076.1098.

11. Mannucci A, Argento FR, Fini E, et al. The Impact of Oxidative Stress in Male Infertility. Front Mol Biosci. 2022 Jan 5;8:799294. doi: 10.3389/fmolb.2021.799294.

12. Kaltsas A. Oxidative Stress and Male Infertility: The Protective Role of Antioxidants. Medicina (Kaunas). 2023 Oct 4;59(10):1769. doi: 10.3390/medicina59101769.

13. Vahedi Raad M, Firouzabadi AM, Tofighi Niaki M, Henkel R, Fesahat F. The impact of mitochondrial impairments on sperm function and male fertility: a systematic review. Reprod Biol Endocrinol. 2024 Jul 17;22(1):83. doi: 10.1186/s12958-024-01252-4.

14. Wang Y, Fu X, Li H. Mechanisms of oxidative stress-induced sperm dysfunction. Frontiers in Endocrinology. 2025 Feb;16:1-15. doi: 10.3389/fendo.2025.1520835.

15. Walczak-Jedrzejowska R, Wolski JK, Slowikowska-Hilczer J. The role of oxidative stress and antioxidants in male fertility. Cent European J Urol. 2013;66(1):60-67. doi: 10.5173/ceju.2013.01.art19.

16. Caroppo E, Dattilo M. Sperm redox biology challenges the role of antioxidants as a treatment for male factor infertility. F&S Reviews. 2022;3(1):90-104. doi: 10.1016/j.xfnr.2021.12.001.

17. Sudhakaran G, Kesavan D, Kandaswamy K, Guru A, Arockiaraj J. Unravelling the epigenetic impact: Oxidative stress and its role in male infertility-associated sperm dysfunction. Reprod Toxicol. 2024 Mar;124:108531. doi: 10.1016/j.reprotox.2023.108531.

18. Silva R, Carrageta DF, Alves MG, Silva BM, Oliveira PF. Antioxidants and Male Infertility. Antioxidants (Basel). 2022 Jun 12;11(6):1152. doi: 10.3390/antiox11061152.

19. Pedre B, Barayeu U, Ezeriņa D, Dick TP. The mechanism of action of N-acetylcysteine (NAC): The emerging role of H2S and sulfane sulfur species. Pharmacol Ther. 2021 Dec;228:107916. doi: 10.1016/j.pharmthera.2021.107916.

20. Sahasrabudhe SA, Terluk MR, Kartha RV. N-acetylcysteine Pharmacology and Applications in Rare Diseases-Repurposing an Old Antioxidant. Antioxidants (Basel). 2023 Jun 21;12(7):1316. doi: 10.3390/antiox12071316.

21. Zhou Z, Cui Y, Zhang X, Zhang Y. The role of N-acetyl-cysteine (NAC) orally daily on the sperm parameters and serum hormones in idiopathic infertile men: A systematic review and meta-analysis of randomised controlled trials. Andrologia. 2021 Mar;53(2):e13953. doi: 10.1111/and.13953.

22. Jannatifar R, Parivar K, Roodbari NH, Nasr-Esfahani MH. Effects of N-acetyl-cysteine supplementation on sperm quality, chromatin integrity and level of oxidative stress in infertile men. Reprod Biol Endocrinol. 2019 Feb 16;17(1):24. doi: 10.1186/s12958-019-0468-9.

23. Mateus FG, Moreira S, Martins AD, Oliveira PF, Alves MG, Pereira ML. L-Carnitine and Male Fertility: Is Supplementation Beneficial? J Clin Med. 2023 Sep 6;12(18):5796. doi: 10.3390/jcm12185796.

24. Ahmed MM, Ibrahim ZS, Alkafafy M, El-Shazly SA. L-carnitine protects against testicular dysfunction caused by gamma irradiation in mice. Acta Histochem. 2014 Jul;116(6):1046-1055. doi: 10.1016/j.acthis.2014.04.010.

25. Oner G, Oner C, Junejo NN. L-carnitine supplementation before assisted reproduction for male infertility. Reproductive biomedicine online. 2024;49(S):104593.

26. Shaikh J, More A, Anjankar N, Nair N, Mahajan SS, Nawale N. Enhancing Male Fertility Through Nutrition: The Role of L-Carnitine in Asthenozoospermic Patients. J Pharm Bioallied Sci. 2025 May;17(Suppl 1):S1019-S1022. doi: 10.4103/jpbs.jpbs_94_25.

27. Wei G, Zhou Z, Cui Y, et al. A Meta-Analysis of the Efficacy of L-Carnitine/L-Acetyl-Carnitine or N-Acetyl-Cysteine in Men With Idiopathic Asthenozoospermia. Am J Mens Health. 2021 Mar-Apr;15(2):15579883211011371. doi: 10.1177/15579883211011371.

28. Khaw SC, Wong ZZ, Anderson R, Martins da Silva S. L-carnitine and l-acetylcarnitine supplementation for idiopathic male infertility. Reprod Fertil. 2020 Dec 23;1(1):67-81. doi: 10.1530/RAF-20-0037.

29. Ranneh Y, Hamsho M, Fadel A, Ali Osman HM, Ali EW, Mohammed Kambal NH. Therapeutic potential of carnitine and N-Acetyl-Cysteine supplementation on sperm parameters and pregnancy outcomes in idiopathic male infertility: A systematic review and meta-analysis of randomised control trials. Reproduction and Breeding. 2025;5(1):74-83. doi: 10.1016/j.repbre.2025.02.002.

30. Boeri L, Fallara G, Pozzi E, et al. The impact of different WHO reference criteria for semen analysis in clinical practice: Who will benefit from the new 2021 thresholds for normal semen parameters? Andrology. 2022 Sep;10(6):1134-1142. doi: 10.1111/andr.13213.

31. Wald G, Punjani N, Hayden R, Feliciano M, Dudley V, Goldstein M. Assessing the clinical value of the Kruger strict morphology criteria over the World Health Organization fourth edition criteria. F S Rep. 2021 Apr 19;2(2):176-180. doi: 10.1016/j.xfre.2021.04.003.

32. Ranganathan P. An Introduction to Statistics: Choosing the Correct Statistical Test. Indian J Crit Care Med. 2021 May;25(Suppl 2):S184-S186. doi: 10.5005/jp-journals-10071-23815.

33. Kwak S. Are Only p-Values Less Than 0.05 Significant? A p-Value Greater Than 0.05 Is Also Significant! J Lipid Atheroscler. 2023 May;12(2):89-95. doi: 10.12997/jla.2023.12.2.89.

34. Safarinejad MR, Safarinejad S. Efficacy of selenium and/or N-acetyl-cysteine for improving semen parameters in infertile men: a double-blind, placebo controlled, randomized study. J Urol. 2009 Feb;181(2):741-751. doi: 10.1016/j.juro.2008.10.015.

35. Ghafarizadeh A, Malmir M, Naderi Noreini S, Faraji T. Antioxidant effects of N-acetylcysteine on the male reproductive system: A systematic review. Andrologia. 2021 Feb;53(1):e13898. doi: 10.1111/and.13898.

36. Baetas J, Raba a A, Gon alves A, Barros A, Sousa M, Sá R. Protective role of N-acetylcysteine (NAC) on human sperm exposed to etoposide. Basic Clin Androl. 2019 Feb 7;29:3. doi: 10.1186/s12610-018-0082-2.

37. Nazari L, Salehpour S, Hosseini S, et al. Effect of antioxidant supplementation containing L-carnitine on semen parameters: a prospective interventional study. JBRA Assist Reprod. 2021 Feb 2;25(1):76-80. doi: 10.5935/1518-0557.20200043.

38. Lahimer M, Gherissi O, Ben Salem N, et al. Effect of Micronutrients and L-Carnitine as Antioxidant on Sperm Parameters, Genome Integrity, and ICSI Outcomes: Randomized, Double-Blind, and Placebo-Controlled Clinical Trial. Antioxidants (Basel). 2023 Oct 31;12(11):1937. doi: 10.3390/antiox12111937.

39. Kooshesh L, Nateghian Z, Aliabadi E. Evaluation of L-Carnitine Potential in Improvement of Male Fertility. J Reprod Infertil. 2023 Apr-Jun;24(2):69-84. doi: 10.18502/jri.v24i2.12491.

40. Micic S, Lalic N, Djordjevic D, et al. Double-blind, randomised, placebo-controlled trial on the effect of L-carnitine and L-acetylcarnitine on sperm parameters in men with idiopathic oligoasthenozoospermia. Andrologia. 2019 Jul;51(6):e13267. doi: 10.1111/and.13267.

41. Ahmadi S, Bashiri R, Ghadiri-Anari A, Nadjarzadeh A. Antioxidant supplements and semen parameters: An evidence based review. Int J Reprod Biomed. 2016 Dec;14(12):729-736.

42. Li KP, Yang XS, Wu T. The Effect of Antioxidants on Sperm Quality Parameters and Pregnancy Rates for Idiopathic Male Infertility: A Network Meta-Analysis of Randomized Controlled Trials. Front Endocrinol (Lausanne). 2022 Feb 21;13:810242. doi: 10.3389/fendo.2022.810242.

43. Dimitriadis F, Borgmann H, Struck JP, Salem J, Kuru TH. Antioxidant Supplementation on Male Fertility-A Systematic Review. Antioxidants (Basel). 2023 Mar 30;12(4):836. doi: 10.3390/antiox12040836.

44. Jannatifar R, Parivar K, Hayati Roodbari N, Nasr-Esfahani MH. The Effect of N-Acetyl-Cysteine on NRF2 Antioxidant Gene Expression in Asthenoteratozoospermia Men: A Clinical Trial Study. Int J Fertil Steril. 2020 Oct;14(3):171-175. doi: 10.22074/ijfs.2020.44411.

45. Zahaki Nosrat F, Yari S, Mahmoodi B, Hasanein P. Effects of N-acetylcysteine on rat sperm treated with hydrogen peroxide in in vitro conditions. Biotech Histochem. 2025 Jul;100(5):303-311. doi: 10.1080/10520295.2025.2516582.

46. Chang D, Kong F, Jiang W, et al. Effects of L-carnitine Administration on Sperm and Sex Hormone Levels in a Male Wistar Rat Reproductive System Injury Model in a High-Altitude Hypobaric Hypoxic Environment. Reprod Sci. 2023 Jul;30(7):2231-2247. doi: 10.1007/s43032-022-00948-5.

47. Jabarineitapeh M, Naderi N, Tavalaee M, Nasr-Esfahani MH. Effects of L-carnitine over-supplementation on spermatogenesis and sperm function in healthy NMRI mice. Tissue Cell. 2025 Jun 14;96:103014. doi: 10.1016/j.tice.2025.103014.

48. Ghorbani F, Nasiri Z, Koohestanidehaghi Y, Lorian K. The antioxidant roles of L-carnitine and N-acetyl cysteine against oxidative stress on human sperm functional parameters during vitrification. Clin Exp Reprod Med. 2021 Dec;48(4):316-321. doi: 10.5653/cerm.2021.04560.

49. Virmani MA, Cirulli M. The Role of l-Carnitine in Mitochondria, Prevention of Metabolic Inflexibility and Disease Initiation. Int J Mol Sci. 2022 Feb 28;23(5):2717. doi: 10.3390/ijms23052717.

50. Lee YG, Chou HC, Chen YT, et al. L-Carnitine reduces reactive oxygen species/endoplasmic reticulum stress and maintains mitochondrial function during autophagy-mediated cell apoptosis in perfluorooctanesulfonate-treated renal tubular cells. Sci Rep. 2022 Mar 18;12(1):4673. doi: 10.1038/s41598-022-08771-3.

51. Padwal LP, More A, Choudhary N, Kalasakar GL, Wadhe T. L-Carnitine and Acetyl-L-Carnitine: A Novel Approach to Treating Male Infertility with Abnormal Sperm Morphology. J Pharm Bioallied Sci. 2025 May;17(Suppl 1):S1038-S1041. doi: 10.4103/jpbs.jpbs_256_25.

52. Ma X, Yang Y, Liu S, Cui Y, Wu J. Meta-analysis of the efficacy and safety of L-carnitine and N-acetylcysteine monotherapy for male idiopathic infertility. Rev Int Androl. 2025 Mar;23(1):1-12. doi: 10.22514/j.androl.2025.004.

53. Iliceto M, Stensen MH, Andersen JM, Haugen TB, Witczak O. Levels of L-carnitine in human seminal plasma are associated with sperm fatty acid composition. Asian J Androl. 2022 Sep-Oct;24(5):451-457. doi: 10.4103/aja2021107.

54. Adeoye O, Olawumi J, Opeyemi A, Christiania O. Review on the role of glutathione on oxidative stress and infertility. JBRA Assist Reprod. 2018 Mar 1;22(1):61-66. doi: 10.5935/1518-0557.20180003.

55. Agarwal A, Sengupta P, Durairajanayagam D. Role of L-carnitine in female infertility. Reprod Biol Endocrinol. 2018 Jan 26;16(1):5. doi: 10.1186/s12958-018-0323-4.

56. Yang K, Wang N, Guo HT, et al. Effect of L-carnitine on sperm quality during liquid storage of boar semen. Asian-Australas J Anim Sci. 2020 Nov;33(11):1763-1769. doi: 10.5713/ajas.19.0455.

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Порівняльне дослідження N-ацетилцистеїну та L-карнітину в лікуванні чоловічого безпліддя (плацебо-контрольоване дослідження)

Резюме. Актуальність. Чоловіче безпліддя — це всесвітньо визнаний стан здоров'я, який спостерігається переважно у віковому діапазоні 35–39 років. У глобальному масштабі чоловіки щонайменше з трьох із шести пар страждають від безпліддя. Дослідницькі дані показують терапевтичні переваги L-карнітину та N-ацетилцистеїну в безплідних чоловіків, однак наявні дані обмежені високою гетерогенністю сучасних досліджень. Тому **метою** було вивчити вплив цих методів лікування на параметри сперми, рівень малонового діальдегіду в ній та загальну антиоксидантну здатність. **Матеріали та методи.** У цьому рандомізованому плацебо-контрольованому клінічному дослідженні з січня 2021 року по грудень 2024 року взяли участь 180 пацієнтів чоловічої статі з нормальним жіночим фактором та ідіопатичною олігоастенотератозооспермією. Особи вікової групи 25–40 років були рандомізовані для лікування L-карнітином (1000 мг перорально), N-ацетилцистеїном (перорально) та плацебо (цукрові пакетики). Базові дані включали вік пацієнта та параметри сперми (рухливість, концентрацію, морфологію сперматозоїдів та об'єм сперми). Параметри сперми в групах були повторно вивчені через шість місяців дослідження. Крім того, загальну антиоксидантну здатність та рівень малонового діальдегіду в спермі оцінювали до та після лікування. **Результати.** Шестимісячний аналіз показав, що параметри сперми, включаючи рухливість сперматозоїдів (38 та 38 проти 4 %), їхню морфологію (30 і 29 проти 7 %) та концентрацію (25 і 24 проти 2 %), значно поліпшилися при застосуванні відповідно N-ацетилцистеїну та L-карнітину порівняно з плацебо. Однак об'єм сперми (6 та 5 проти 4 %) не зазнав впливу жодного з методів лікування й суттєво не відрізнявся від групи плацебо ($p > 0,05$). Порівняно з попереднім лікуванням монотерапія N-ацетилцистеїном поліпшила загальну антиоксидантну здатність ($1,92 \pm 0,12$ проти $2,61 \pm 0,12$; $p = 0,01$) та знизила рівень малонового діальдегіду ($2,46 \pm 0,11$ проти $1,85 \pm 0,10$; $p = 0,01$) у спермі. Однак порівняно з плацебо ці поліпшення не спостерігалися при монотерапії L-карнітином. **Висновки.** Пероральне лікування L-карнітином та N-ацетилцистеїном ефективно поліпшувало концентрацію, морфологію та рухливість сперматозоїдів у чоловіків із безпліддям. Однак при використанні N-ацетилцистеїну та L-карнітину як монотерапії статистично значущих відмінностей не було. Крім того, N-ацетилцистеїн виявився кращим за L-карнітин у зниженні оксидативного стресу та рівня малонового діальдегіду в плазмі сперми. Проспективні дослідження повинні визначити механізми, що лежать в основі ефективності L-карнітину/N-ацетилцистеїну, та оцінити безпеку й ефективність комбінованого антиоксидантного лікування чоловічого безпліддя.

Ключові слова: чоловіче безпліддя; N-ацетилцистеїн; L-карнітин; рухливість; морфологія; загальна антиоксидантна здатність; малоновий діальдегід; сперматозоїди; сперма