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Assessment of L-carnitine as a therapeutic agent for cancer-related fatigue in patients receiving platinum-based chemotherapy regimens; a parallel-group, randomized, double-blind clinical trial study

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Abstract

Introduction: Cancer-related fatigue (CRF) is a common and debilitating symptom that significantly impacts patients' quality of life and daily functioning. L-carnitine, a naturally occurring amino acid derivative involved in energy metabolism, has been suggested as a potential therapeutic agent to alleviate fatigue.
Objectives: This study aimed to assess the effectiveness of L-carnitine supplementation in fatigue management among cancer patients.
Patients and Methods: This randomized, double-blind clinical trial conducted at Imam Hossein hospital enrolled 90 cancer patients receiving platinum-based chemotherapy between September 2024 and June 2025. Participants were randomly assigned to receive either L-carnitine or a placebo, with 45 patients in each group. Eligible patients were over 18 years, experiencing fatigue, and provided informed written consent. Demographic and clinical data were collected by a trained researcher who was blinded to the group allocation. Fatigue levels were assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire at baseline, and at four and eight weeks. The primary outcome was the comparison of FACIT-F scores both between and within the L-carnitine and control groups throughout the study.
Results: The study results showed that although the fatigue scores were similar between the L-carnitine and control groups at baseline, the L-carnitine group experienced a significantly greater improvement in fatigue over time. By the fourth week, participants receiving L-carnitine exhibited significantly higher improvements in fatigue scores compared to the control group, and this advantage was even more pronounced by the eighth week. Additionally, the L-carnitine group continued to show a meaningful increase in fatigue score improvements between the fourth and eighth weeks, while the control group's scores remained relatively stable during that period.
Conclusion: L-carnitine appears to be a safe and promising adjunctive therapy for managing CRF in patients receiving platinum-based chemotherapy. Incorporation of L-carnitine supplementation into supportive care protocols may improve patient outcomes and quality of life.
Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials with code (identifier: IRCT20241112063688N1; https://irct.behdasht.gov.ir/trial/80160), and ethical code from Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1403.289; https://ethics.research.ac.ir/EthicsProposalView.php?id=492026).

Introduction

Platinum-based chemotherapy regimens, comprising cisplatin, carboplatin, and oxaliplatin represent cornerstone therapeutic interventions in the management of various malignancies and have been extensively utilized in clinical oncology for nearly three decades (1,2). These agents exert

Key point

In this randomized, double-blind clinical trial study, we found that L-carnitine supplementation leads to significantly greater and progressively increasing improvements in fatigue among cancer patients compared to controls, with notable benefits emerging by the fourth week and continuing through the eighth week.

their anticancer effects primarily through covalent DNA adduct formation, which leads to intrastrand crosslinks that interfere with DNA repair mechanisms, ultimately triggering apoptosis in cancer cells (3). The widespread clinical application of platinum compounds stems from their demonstrated efficacy across diverse cancer types, including ovarian, lung, testicular, bladder, head and neck, and colorectal cancers (4). Recent systematic reviews and meta-analyses have consistently demonstrated that platinum-based regimens significantly improve pathological complete response rates and overall survival compared to non-platinum alternatives, particularly in triple-negative breast cancer, where platinum-containing chemotherapy achieved response rates of 62.7% versus 43.1% for platinum-free regimens (5). However, the therapeutic benefits of these agents are frequently accompanied by significant dose-limiting toxicities, including nephrotoxicity, neurotoxicity, ototoxicity (6), and myelosuppression, which can compromise treatment adherence and patient quality of life (1,7).

Cancer-related fatigue (CRF) represents the most prevalent and debilitating symptom experienced by oncology patients, affecting approximately 80% of individuals receiving chemotherapy (8) and persisting in up to 50% of cancer survivors years after treatment completion (9). Unlike normal fatigue, CRF is characterized by a persistent, subjective sense of exhaustion that is disproportionate to recent activity and significantly impairs physical, cognitive, and psychosocial functioning (8,10). The pathophysiology of CRF is multifactorial, involving dysregulation of inflammatory cytokines (particularly tumor necrosis factor-α and interleukin-6), mitochondrial dysfunction, oxidative stress, and disruption of cellular energy metabolism (11,12). Chemotherapy-induced fatigue specifically results from the toxic effects of cytotoxic agents on non-targeted tissues, including skeletal muscle, where oxidative stress leads to compromised cellular function and reduced exercise tolerance (12). Clinical assessment studies have consistently demonstrated that CRF severity correlates with decreased performance status, increased symptom burden, and reduced treatment efficacy (11,13).

L-carnitine, a naturally occurring quaternary ammonium compound, plays a fundamental role in cellular energy metabolism by facilitating the transport of long-chain fatty acids across the mitochondrial membrane for β-oxidation (14). This essential metabolic function makes L-carnitine critical for maintaining cellular energy homeostasis, particularly in metabolically active tissues such as cardiac and skeletal muscle (15-17). In cancer patients, several chemotherapeutic agents, including cisplatin and ifosfamide, have been shown to interfere with carnitine absorption, synthesis, and renal excretion, leading to secondary carnitine deficiency that may contribute to treatment-related fatigue and functional decline (18). Preliminary clinical investigations have suggested that carnitine deficiency may play a contributory role in the development of chemotherapy-induced fatigue, with restoration of carnitine pools through supplementation demonstrating potential benefits in improving fatigue scores and quality of life parameters (17, 19). However, recent systematic reviews and meta-analyses have yielded conflicting results regarding the efficacy of L-carnitine supplementation for CRF, showing no significant improvement (14), leading to current American Society of Clinical Oncology (ASCO) guidelines recommending against L-carnitine supplementation for CRF management (20).

Objectives

The objective of this study is to assess the effectiveness of L-carnitine supplementation on fatigue symptoms in cancer patients by comparing the changes in fatigue severity between the L-carnitine and placebo groups throughout the treatment period in a parallel, double-blind, randomized controlled trial.

Patients and Methods

Study design and participants

This parallel, randomized, double-blind clinical trial was conducted at Imam Hossein hospital in Tehran, Iran, from September 2024 to June 2025. The study enrolled 110 patients with cancer who were receiving platinum-based chemotherapy regimens. Eligible participants were randomly assigned to receive either L-carnitine supplementation (n = 45) or a placebo (n = 45), with both participants and researchers blinded to group allocation. The trial aimed to evaluate the effects of L-carnitine on CRF over eight weeks.

Inclusion and exclusion criteria

The inclusion criteria for this clinical trial were adult patients (>18 years) diagnosed with cancer who were receiving platinum-based chemotherapy regimens at Imam Hossein hospital, with a baseline fatigue score indicating the presence of fatigue, and who provided informed written consent to participate in the study. Exclusion criteria included patients with known hypersensitivity to L-carnitine, those currently taking supplements or medications known to affect fatigue, individuals with significant comorbidities such as severe liver or kidney dysfunction, active infections, or psychiatric disorders, as well as pregnant or breastfeeding women. Patients who were unable to comply with the study protocol or provide

informed consent were also excluded to ensure the safety and integrity of the trial.

Sample size

The sample size was calculated based on detecting a clinically significant difference in fatigue scores between the L-carnitine and placebo groups, with a power of 80% and a significance level of 0.05. Assuming an expected effect size derived from previous studies on fatigue reduction, and accounting for potential dropout rates, a total of 90 participants (45 per group) was determined to be sufficient to provide adequate statistical power.

Randomization/allocation

Participants were randomly assigned to either the L-carnitine or placebo group using a computer-generated randomization sequence. Randomization was conducted in blocks to maintain group balance throughout the enrollment period. Allocation concealment was achieved by using sealed, opaque envelopes prepared by an independent third party, preventing both participants and researchers from knowing the treatment assignments until the conclusion of the study.

Blinding

In this double-blind clinical trial, both the participants and the researchers administering the treatments were unaware of group assignments to prevent bias. The L-carnitine and placebo capsules were identical in appearance, taste, and packaging, and were labeled with codes by an independent pharmacist not involved in the study. These codes were only revealed after the data analysis was completed, ensuring that neither the patients nor the study researchers could influence the outcomes based on knowledge of the treatment allocation.

Intervention

Participants were randomly assigned in a parallel-group design to receive either L-carnitine supplementation or a placebo for the duration of the study. The L-carnitine group received a specified dose of L-carnitine (1 g/day oral liquid of L-carnitine) orally daily starting at baseline and continuing for eight weeks alongside their ongoing platinum-based chemotherapy regimen. The placebo group received an identical-appearing inert substance administered with the same schedule (21).

Data collection

Data collection for this clinical trial involved obtaining written informed consent from all participants, followed by a comprehensive gathering of demographic and clinical information. Fatigue levels were assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire at baseline, and subsequently at the fourth and eighth weeks of the intervention. Demographic and clinical data, including age, gender, underlying diseases, cancer type, tumor grade, cancer duration, presence of metastasis, and chemotherapy duration, were collected through participant interviews and clinical assessments conducted by the researcher. To minimize bias, all data were collected by a trained researcher who was blinded to the group allocation. Study outcomes were meticulously recorded in secure, standardized case report forms, while adherence to the supplementation regimen was monitored through patient self-reports and pill counts during follow-up visits.

Validity of FACIT-F questionnaire

Patients were assessed with the FACIT-F questionnaire, which is a 13-item self-reported tool evaluating fatigue experienced during usual daily activities over the past week. The 13 items are divided into two domains: Experience (5 items), which assess perceptions and severity of fatigue feelings, and Impact (8 items), which measure how fatigue affects daily functioning. Each item is scored on a 5-point Likert scale from 0 (“not at all”) to 4 (“very much”), with negatively phrased items reverse scored. Scores are summed to yield a total score ranging from 0 to 52, where a higher score indicates less fatigue. The FACIT-F questionnaire has demonstrated strong psychometric properties such as excellent internal consistency (Cronbach’s alpha $\geq$ 0.88), good test-retest reliability, and convergent validity with other patient-reported outcomes (22, 23). Its validity and reliability in the Iranian population were further confirmed, demonstrated by a Cronbach’s alpha coefficient of 0.92 (24).

Outcomes

The primary outcome of this study was the comparison of changes in FACIT-F questionnaire scores both between and within the groups of patients who received L-carnitine and those who received a placebo over the eight-week study period. The secondary outcome focused on evaluating the effectiveness of L-carnitine as a therapeutic agent in alleviating CRF and enhancing patients’ overall quality of life.

Statistical analysis

Data were analyzed using statistical package for social sciences (SPSS) Statistics version 27 (IBM Corp., USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Based on the distribution, parametric or non-parametric tests were applied for between-group comparisons of quantitative variables: the independent t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables were compared using the chi-square test or Fisher’s exact test when appropriate. Within-group comparisons of normally distributed quantitative data over the baseline, 4- and 8-week time points were conducted using repeated measures analysis of variance (ANOVA) and paired t-tests. A *P* value of less than 0.05 was considered statistically significant.

Results

Initially, 136 individuals were assessed for eligibility in the study. Of these, 18 were excluded, with 11 not meeting the inclusion criteria and 7 declining to participate. Consequently, 118 participants were randomized into two groups; 49 allocated to the L-carnitine group, all of whom received the allocated L-carnitine, and 49 allocated to the control group, all of whom received the allocated placebo. In the L-carnitine group, 2 participants were lost to follow-up, and 2 were excluded from analysis due to non-adherence to L-carnitine consumption, resulting in 45 participants analyzed. In the control group, 4 participants were lost to follow-up, with no exclusions from the analysis, resulting in 45 participants analyzed (Figure 1).

The comparison between the L-carnitine and control groups revealed no significant difference in gender distribution, with a slightly higher proportion of females in the control group and males in the L-carnitine group. Underlying diseases such as chronic obstructive pulmonary disease, diabetes, hypertension, and hyperthyroidism were similarly distributed across both groups, with a notable proportion of participants having no underlying disease. Cancer types varied between groups, with a significant difference observed; breast cancer was relatively balanced, whereas colon and rectum cancers were more common in the L-carnitine group, and lung and ovarian cancers were more frequent in the control group. Tumor grading showed similar distributions across both groups, without significant differences among the various grades. The presence or absence of metastasis was comparable between groups. Cancer duration and chemotherapy duration were alike in both groups, as was the age of participants. Overall, aside from the variation in cancer types, the demographic characteristics and baseline clinical data did not differ significantly between the L-carnitine and control groups (Table 1).

The comparative analysis of FACIT-F questionnaire scores between the L-carnitine and control groups over the course of the study indicated no significant difference at baseline. However, by the fourth week, the L-carnitine group showed a markedly higher improvement in fatigue scores compared to the control group, a statistically significant difference. This trend continued and was even more pronounced at the eighth week, with the L-carnitine group maintaining substantially better fatigue scores than the control group, demonstrating significant benefits in fatigue reduction associated with L-carnitine treatment over time (Table 2).

Within-group comparisons of FACIT-F questionnaire scores over the study period showed significant improvements in both the L-carnitine and control groups. In the L-carnitine group, scores increased substantially

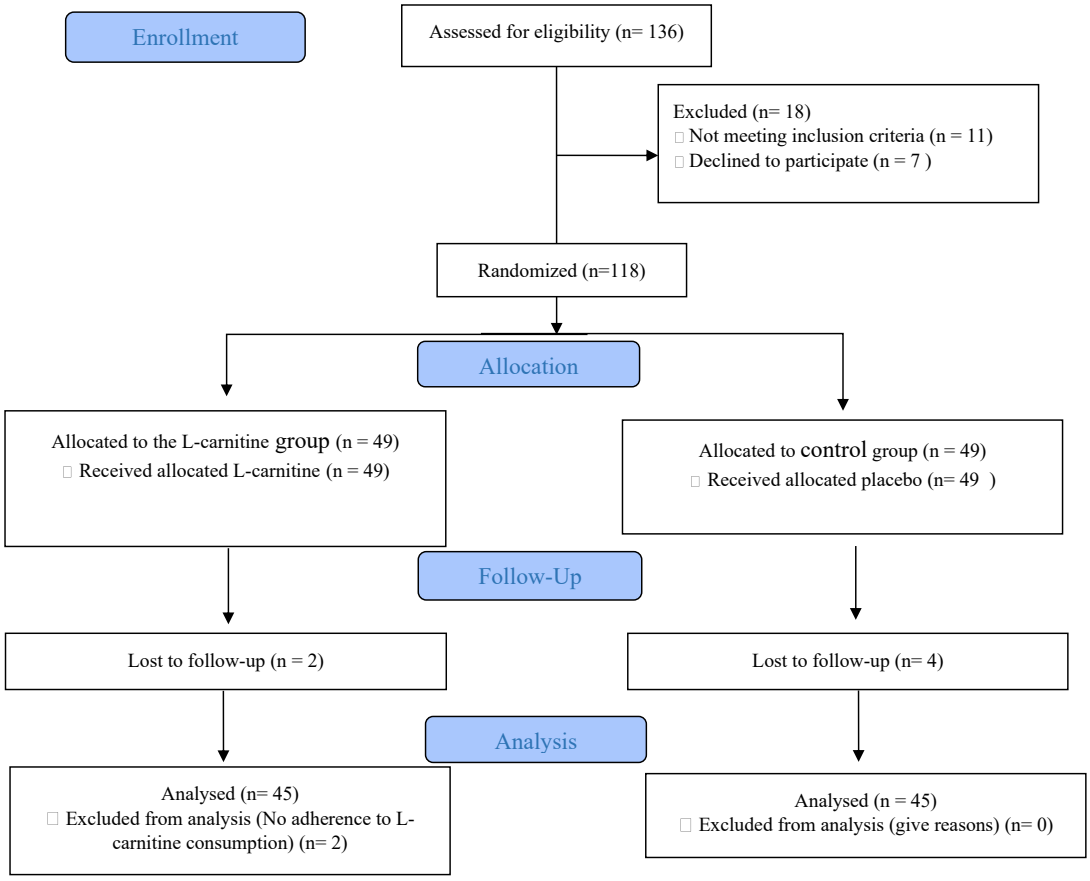

Figure 1. CONSORT Flow diagram of the study.

Table 1. Comparison of demographic characteristics and baseline clinical data between the two groups

Variables		Group			*P* value
		L-carnitine (n = 45)	Control (n = 45)	Total (n = 90)	
Gender, N (%)	Female	20 (44.44)	26 (57.78)	46 (51.11)	0.206*
	Male	25 (55.56)	19 (42.22)	44 (48.89)	
Underlying diseases, N (%)	COPD	11 (24.44)	4 (8.89)	15 (16.67)	0.159**
	Diabetes	6 (13.33)	8 (17.78)	14 (15.56)	
	Hypertension	13 (28.89)	10 (22.22)	23 (25.56)	
	Hyperthyroidism	0 (0.0)	1 (2.22)	1 (1.11)	
	None	15 (33.33)	22 (48.89)	37 (41.11)	
Cancer type, N (%)	Breast	11 (24.44)	9 (20.0)	20 (22.22)	0.003*
	Colon	12 (26.67)	3 (6.67)	15 (16.67)	
	Rectum	9 (20.0)	3 (6.67)	12 (13.33)	
	Lung	9 (20.0)	16 (35.56)	25 (27.78)	
	Ovarian	4 (8.89)	14 (31.11)	18 (20.0)	
Tumor grading	Grade 1	12 (26.67)	14 (31.11)	26 (28.89)	0.930*
	Grade 2	12 (26.67)	13 (28.89)	25 (27.78)	
	Grade 3	11 (24.44)	9 (20.0)	20 (22.22)	
	Grade 4	10 (22.22)	9 (20.0)	19 (21.11)	
Metastasis, N (%)	No	35 (77.78)	36 (80.0)	71 (78.89)	0.796*
	Yes	10 (22.22)	9 (20.0)	19 (21.11)	
Cancer duration (month; Median [IQR])		6 (3 – 8)	4 (2 – 8)	5 (2 – 8)	0.333***
Chemotherapy duration (month; Median [IQR])		5 (4 – 6)	5 (4 – 6)	5 (4 – 6)	0.230***
Age (year; Median [IQR])		54 (47 – 63)	60 (49 – 64)	56.5 (47 – 64)	0.243***

COPD: Chronic obstructive pulmonary disease; IQR: Interquartile range (Q1 – Q3).
*Chi-square, **Fisher's exact test, ***Mann-Whitney U.

Table 2. Comparative analysis of the FACIT-F questionnaire scores between the control and L-carnitine groups during the study

Time	Treatment groups				Mean difference	95% CI		*P* value
	L-carnitine		Control					
	Mean	SD	Mean	SD		Lower	Upper	
Baseline	16.71	3.21	17.37	2.35	0.66	-1.84	0.51	0.265*
Fourth week	44.22	2.67	18.33	1.91	25.89	24.91	26.86	<0.001*
Eighth week	45.97	1.98	18.35	1.56	27.62	26.87	28.37	<0.001*

SD: Standard deviation; CI: Confidence interval. *Independent T-test.

from baseline through the fourth and eighth weeks, with significant differences observed between all-time points, indicating a progressive improvement in fatigue levels over time. Similarly, the control group experienced a smaller yet statistically significant increase in scores from baseline to both the fourth and eighth weeks, though there was no meaningful change between the fourth and eighth weeks. These findings highlight a marked and consistent improvement in fatigue in the L-carnitine group throughout the study, compared to a more modest and plateaued improvement in the control group (Table 3 and Figure 2).

The comparative analysis of changes in FACIT-F questionnaire scores between the L-carnitine and control groups at different measurement times revealed significant differences in fatigue improvements. From baseline to the fourth week, the L-carnitine group exhibited a substantially greater increase in fatigue scores compared to the control group. This significant difference was also evident from baseline to the eighth week, with the L-carnitine group showing a much larger improvement. Additionally, between the fourth and eighth weeks, the L-carnitine group demonstrated a modest but statistically significant further increase in scores, whereas the control group showed minimal change. These results indicate that L-carnitine treatment led to significantly greater and sustained improvements in fatigue over the study period compared to the control (Table 4).

Table 3. Comparison of FACIT-F questionnaire scores within groups (L-carnitine/control) during the study

Treatment group	Study time						*P* value
	Baseline		Fourth week		Eighth week		
	Mean	SD	Mean	SD	Mean	SD	
L-carnitine	16.71	3.21	44.22	2.67	45.97	1.98	<0.001*
Control	17.37	2.35	18.33	1.91	18.35	1.56	0.009*

Study time			Mean difference	95 % CI		*P* value
				Lower	Upper	
L-carnitine	Baseline	Fourth week	27.51	26.22	28.79	<0.001**
		Eighth week	29.26	28.00	30.52	<0.001**
	Fourth week	Eighth week	1.75	0.87	2.63	<0.001**
Control	Baseline	Fourth week	0.95	0.27	1.60	0.007**
		Eighth week	0.97	0.25	1.69	0.009**
	Fourth week	Eighth week	0.02	-0.66	0.71	0.949**

SD: Standard deviation; CI: Confidence interval. *Repeated measure ANOVA, **Paired T-test.

Discussion

Our results showed that L-carnitine supplementation leads to significantly greater and progressive improvements in CRF, with patients receiving L-carnitine showing marked reductions in fatigue severity over time compared to the control group. These findings suggest that L-carnitine may offer a valuable therapeutic benefit in managing fatigue symptoms in cancer patients, improving their overall quality of life and daily functioning during treatment. These results contrast with several studies in the literature. The large phase III trial by Cruciani et al, involving 376 cancer patients receiving 2 g/d of L-carnitine for four weeks, found no statistically significant differences between treatment and placebo groups in fatigue scores measured by both the brief fatigue inventory and FACIT-F instruments, despite improvements in both arms compared to baseline (25). A subsequent systematic review and meta-analysis by Marx et al examining twelve studies found that carnitine supplementation did not significantly reduce CRF, with a standardized mean difference of 0.06 points, and concluded that results from studies with lower risk of bias do not support carnitine use for CRF (14). Similarly, the cooperative oncology group's phase III randomized, double-blind, placebo-controlled trial found no statistically significant differences between the L-carnitine and placebo arms for fatigue improvement (26). Watanabe et al also found that L-carnitine supplementation did not provide any benefit in alleviating chemotherapy-related fatigue in patients with gastric cancer (27). However, some studies have reported positive outcomes, including a study by Matsui et al involving 11 cancer patients experiencing general fatigue during a chemotherapy regimen, found

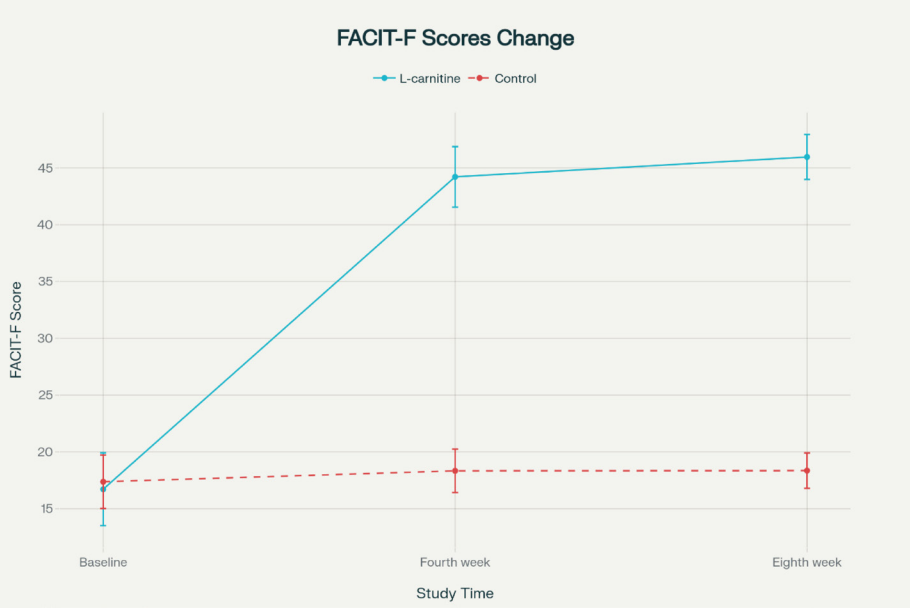

Figure 2. Trend of FACIT-F questionnaire scores changes in the L-carnitine and control groups during the study. FACIT-F; Functional assessment of chronic illness therapy – fatigue

Table 4. Comparative analysis of FACIT-F questionnaire score changes between the control and L-carnitine at three measurement times

Measurement time	Treatment groups				Mean difference	95% CI		*P* value
	L-carnitine		Control					
	Mean	SD	Mean	SD		Lower	Upper	
Baseline & Fourth week	27.51	4.28	0.95	2.26	26.56	25.12	27.99	<0.001*
Baseline & Eighth week	29.26	4.20	0.97	2.39	28.29	26.85	29.72	<0.001*
Fourth week & Eighth week	1.75	2.91	0.02	2.30	1.73	0.63	2.83	0.002*

SD: Standard deviation; CI: Confidence interval. *Independent T-test.

that L-carnitine supplementation alleviated fatigue in all participants (28). In a study involving patients with head and neck cancer, Endo et al demonstrated that administering L-carnitine helps enhance health-related quality of life (21). Our findings also align with the study by Graziano et al, who reported that L-carnitine supplementation improved chemotherapy-induced fatigue in non-anemic cancer patients with low plasma carnitine levels (18). The key distinction between our study and previous negative results studies appears to be our specific focus on platinum-based chemotherapy patients, a population with well-documented carnitine depletion and mitochondrial dysfunction, and our extended eight-week assessment period that captured the progressive nature of L-carnitine's therapeutic benefits.

The apparent efficacy of L-carnitine in this study may be attributed to several methodological factors that differentiate it from previous negative result studies. Earlier positive studies, such as those by Graziano et al (4 g daily) (18), Cruciani et al (2 g daily) (25), and more recent investigations (28), specifically enrolled patients with documented carnitine deficiency or used higher doses, suggesting that patient selection criteria and dosing regimens may be critical determinants of treatment success. The conflicting results in the literature may also reflect differences in cancer types, chemotherapy regimens, baseline carnitine status, and study duration, as evidenced by positive outcomes in specific populations such as head and neck cancer patients receiving cisplatin-based therapy (21) and non-anemic cancer patients receiving chemotherapy (18). Additionally, recent studies have identified L-carnitine as a potential complementary approach for CRF management, though emphasizing the need for more rigorous methodology in future trials (21,27-29). The progressive improvement observed through week 8 in this study aligns with emerging evidence (21) suggesting that longer treatment durations may be necessary to achieve sustained benefits, as carnitine's role in mitochondrial energy metabolism and fatty acid oxidation requires time for physiological restoration.

Overall, while this study reports promising results for L-carnitine supplementation in platinum-based chemotherapy recipients, the findings must be interpreted cautiously, given the substantial body of high-quality evidence showing no benefit from carnitine supplementation for CRF. The discrepancy between these results and the large randomized controlled trials, including the definitive 376-patient study by Cruciani et al (25) and the comprehensive meta-analysis by Marx et al (14), highlights the importance of patient selection, baseline carnitine status assessment, and optimal dosing strategies in future research. Therefore, while these results contribute to the evolving understanding of L-carnitine's potential role in CRF management, particularly in platinum-treated patients, larger multi-center trials with careful attention to baseline carnitine deficiency, standardized dosing protocols, and longer follow-up periods are essential to definitively establish its therapeutic value and inform evidence-based clinical recommendations.

Conclusion

The results demonstrate that L-carnitine supplementation significantly improves CRF in patients treated with platinum-based chemotherapy regimens. The sustained improvement observed throughout the eight weeks suggests that L-carnitine could serve as a long-term beneficial adjunctive therapy for fatigue management in this patient population. Given the profound impact of CRF on patient quality of life, incorporating L-carnitine supplementation may enhance supportive care strategies for cancer patients. Further investigations are recommended to explore optimal dosing, long-term effects, and underlying mechanisms of L-carnitine's efficacy in CRF alleviation.

Limitations of the study

The relatively short follow-up period of eight weeks may not capture the long-term effects of L-carnitine supplementation on CRF. The sample size, while adequately powered for the primary outcome, was limited and may not fully represent the diverse population of cancer patients receiving platinum-based chemotherapy. Additionally, the study was conducted at a single center, which could limit the generalizability of the findings to other settings or populations. Variability in cancer types and treatment regimens among participants may also have influenced the results. Lastly, reliance on self-reported fatigue measures may introduce subjective bias despite the use of validated questionnaires.

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facilities to conduct this study. We also gratefully acknowledge Shahid Beheshti University of Medical Sciences for their approval, guidance, and continuous support throughout the research.

Authors' contribution

Conceptualization: Sina Homaee, Parisa Delkash, and Farnaz Saberian.
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Investigation: Sina Homaee, Parisa Delkash, and Farnaz Saberian.
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Project management: Farnaz Saberian and Mahmoud Dehghani-ghorbi.
Resources: All authors.
Supervision: All authors.
Validation: Zahra Abbasi and Parisa Delkash.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

None to be declared.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Perplexity.ai and Grammarly.com) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was conducted at Imam Hossein Hospital and is derived from the thesis work of Ali Parsa (Thesis#43010702), with the Ethical code (IR.SBMU.MSP.REC.1403.289), approved by the Shahid Beheshti University of Medical Sciences, Tehran, Iran. The study protocol was also registered as a clinical trial at the Iranian Registry of Clinical Trials (identifier: IRCT20241112063688N1). Accordingly, written informed consent was taken from all participants before any intervention. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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