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Effects of high-dose L-carnitine supplementation on diaphragmatic function in patients with respiratory failure: A randomized clinical trial

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ABSTRACT

Objectives: Evaluation of diaphragmatic function by bedside ultrasound provides information on the degree of disability and the response to treatment intervention in respiratory failure patients with associated respiratory muscle fatigue. This study aimed to assess the impact of high and low-dose L-carnitine supplementation on diaphragmatic muscle function.

Methods: This was a prospective, randomized, controlled clinical trial (trial registration number NCT05322447), for which approval was obtained from our institutional ethics committee (R80/2021). Participating patients were randomly assigned to two groups of 30 patients each. In the low-dose group, L-carnitine was administered at a dose of 6 g/day. The high-dose group received an intravenous infusion of 18 g/day of L-carnitine. On days 0, 3, and 7, diaphragmatic function was assessed by ultrasound, and serum levels of L-carnitine were measured.

Results: Both diaphragmatic excursion (DE) and diaphragmatic thickening fraction (DTf) measurements were positively correlated with serum L-carnitine levels (+r = 0.58 and +r = 0.61, respectively; $p < 0.001$). High-dose L-carnitine independently influenced the DE only, both in an unadjusted model ($p = 0.04$) and after adjustment for age and sex ($p = 0.02$). However, it had no significant effect on DTf, either before ($p = 0.25$) or after ($p = 0.17$) adjustment.

Conclusion: Serum levels of L-carnitine are positively correlated with the two measures of diaphragmatic function (DE and DTf). Moreover, high-dose L-carnitine supplementation had rapid and significant positive effects on DE. This improvement indirectly enhanced patient outcomes and resulted in shorter stays in the Intensive Care Unit and hospital.

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L-carnitine; respiratory failure; ultrasound; diaphragmatic excursion; diaphragmatic thickness fraction; critically ill

1. Introduction

Carnitine is a nutrient essential for the metabolism of fatty acids and their conversion into energy. The primary physiological function of L-carnitine is to move long-chain fatty acids from the cytoplasm to the mitochondrial matrix, where they can be B oxidized[1]. Adequate intracellular carnitine concentrations are vital for optimal fatty acid metabolism in the human body, which uses fatty acids as an energy source. The highest levels of L-carnitine are seen in the skeletal muscles and myocardium[2]. Previous research has shown that L-carnitine supplements improve muscle performance. Nearly two-thirds of hemodialysis patients who experienced cramps, pain, or muscle weakness reported at least some improvement in their symptoms after L-carnitine treatment[3]. L-carnitine has also been found to increase low left ventricular ejection fraction (LVEF) in hemodialysis patients with cardiac morbidity[4]. Studies have also demonstrated that L-carnitine can enhance muscle performance and exercise capacity in athletes [5,6]. Jones et al. assessed the impact of small, medium, and large dose L-carnitine supplementation on organ function in septic shock. [7]

This study aimed to assess the impact of high and low-dose L-carnitine supplementation on diaphragmatic muscle function and subsequent clinical outcomes in critically ill, non-mechanically ventilated patients with respiratory failure (RF).

2. Methods

This was a prospective, randomized, clinical trial performed in the Intensive Care Unit (ICU) of Ain Shams university hospital and was conducted between April and October 2022 in accordance with the Helsinki Declaration of 2013, with clinical trial registration (NCT05322447). The ethical approval was obtained from Institute Ethics Committee with letter no. R80/2021, on the date of 23/5/2021.

All patients or their legal guardians provided informed consent to participation and publication.

The inclusion criteria were to be aged ≥ 21 years, having RF, either due to illness or after surgery that did

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not require invasive mechanical ventilation. Both sexes were included. Patients with diaphragmatic paralysis, end-stage liver disease, hypothyroidism, seizures, on routine dialysis due to liver failure, and those with an allergy to L-carnitine, pivampicillin, or other pivalate-conjugated antibiotics were excluded from the study.

Patients were evaluated for diaphragmatic function upon admission to the ICU using the ultrasonography technique described below, and in patients who consented to participation in the study; serum L-carnitine levels were measured. Patient management was conducted according to ICU protocols, with the maintenance of adequate nutrition and normal electrolyte levels.

A computer-generated list was used to randomly assign patients into two groups of 30 patients.

In the low-dose group, L-carnitine was administered intravenously at a dose of 6 g/day to maintain normal levels (a normal level of serum L-carnitine is in the range of 34–78 nmol/mL)[8]. In the high-dose group, a continuous intravenous infusion of 18 gm/day of L-carnitine was administered to raise plasma levels to double their normal levels in the high-dose group[7]. Serum levels of L-carnitine were measured on days 0 (before L-carnitine was administered), 3, and 7. A sample of 1 mL of blood was collected in a sodium heparin tube, which was then subjected to centrifugation for 10 minutes. L-carnitine levels in the plasma were determined by enzyme-linked immunosorbent assay (ELIZA). Ultrasound assessments of diaphragmatic function were performed on days 0, 3, and 7 using a Hitachi Aloka Prosound Ultrasound System (Hitachi, Ltd., Higashi-Ueno, Taito-Ku, Tokyo, Japan). The ultrasound footage was preserved for analysis and comparison purposes. The assessments measured diaphragmatic excursion (DE) and diaphragm thickness (DT). Two-dimensional or M mode ultrasonography with a 2.5–6 MHz low-frequency curved probe was used to measure the excursion of each hemidiaphragm (Figures 1A, B). DT was measured using B-mode ultrasonography and a 6–13 MHz high-frequency linear probe. For the latter, measurements were taken at the end of inspiration and expiration, and the diaphragmatic thickening fraction (DTf) was determined (Figures 1C, D). The primary outcome of the study was diaphragmatic function on day 7, as determined by the ultrasonography assessment.

If a participating patient's chest condition worsened before day 7, necessitating mechanical ventilation and endotracheal intubation, the patient's data were excluded from the final analysis. L-carnitine is generally well tolerated; however, symptomatic treatment according to ICU protocol was added because L-carnitine can cause some adverse digestive effects. These include diarrhea, vomiting, nausea, and stomach cramping. A "fishy" body odor is also an occasional side effect.

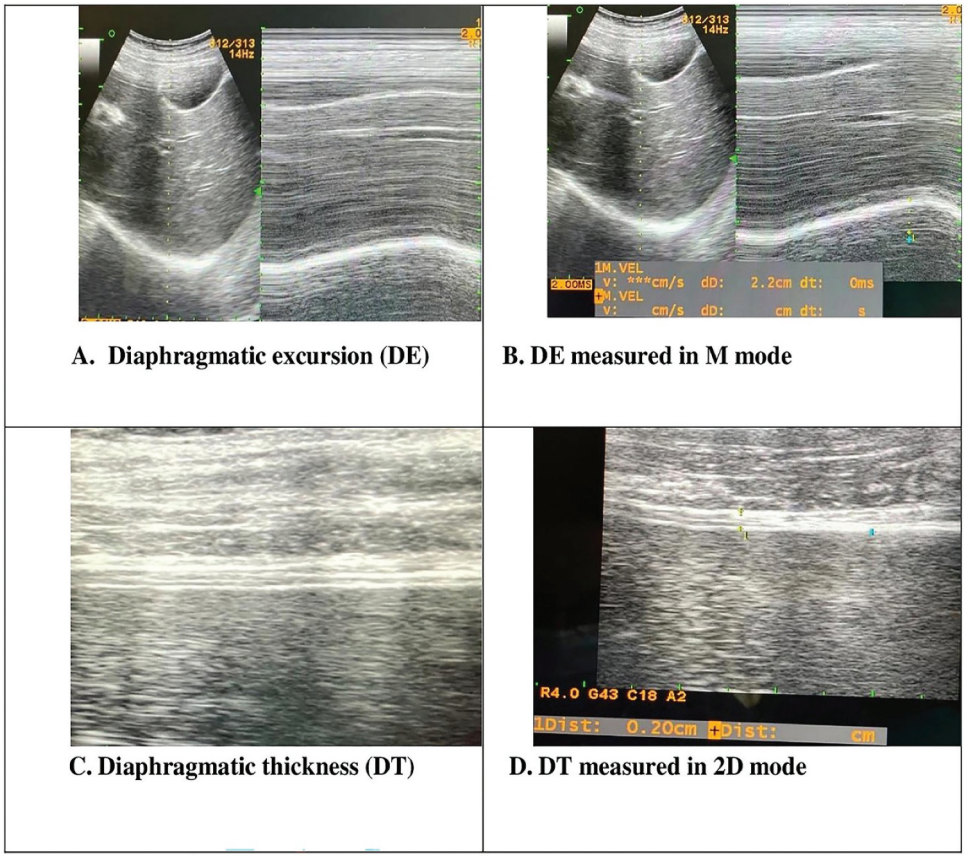

Figure 1. M-mode and 2D-mode ultrasonographic images of diaphragmatic function.
A, B: Diaphragmatic excursions (D) Ein 2D, and M-Modes
C, D: Diaphragmatic thickness (DT), and thickening fraction in 2D -Mode

3. Sample size

G*Power software (version 3.1.0) was used to determine the necessary sample size.

The main goal of the investigation was to compare the mean diaphragmatic function measurements between the two research groups. Allowing for a 20% dropout rate, a sample size of 30 patients per group (60 total) was found to be required to detect an effect size (d) of 0.8 for the primary outcome, with assumptions of a type I error of 0.05 and 80% power.

4. Statistical analysis

Data were collected and tabulated for statistical analysis using Minitab 17.1.0.0 for Windows (Minitab Inc., 2013, PA, USA). Continuous data were presented as means and standard deviations (SD), categorical data were presented as numbers and percentages (%), and the normality of data was determined using the Shapiro-Wilk test. Comparisons between two means were performed using independent t-tests and comparisons between multiple means were performed using one-way ANOVAs with Tukey's post-hoc tests. Chi-square tests were used for frequency comparisons. Linear correlations were identified using Pearson's correlation coefficient. For correlations, a + or − symbol was used before the "r" to indicate the direction of the relationship. To examine the relationship between L-carnitine levels and diaphragmatic motility, we used multiple linear regression, both unadjusted and with adjustments for age and sex. All tests were two-sided and $p < 0.05$ was considered statistically significant.

5. Results

The baseline characteristics of the two groups are summarized in Table 1. The mean (SD) age of patients was 55(±15) years, and more patients were male (61.67%) than female. More than half of the patients (53.33%) had type I RF (RF I) as a consequence of COPD or pneumonia, which presented in 30% and 23% of cases, respectively.

On day 0, before treatment began, the prevalence of L-carnitine deficiency in patients with RF was found to be 23.33%, and the mean (SD) level of serum L-carnitine of all 60 patients was 44.85 (±11.62) nmol/mL (Table 1), and there was no significant difference between mean L-carnitine levels between groups ($p = 0.87$). After administration of L-carnitine, serum L-carnitine levels were significantly elevated in the high-dose group on days 3 and 7 ($p < 0.001$). In the low-dose group, there was non-significant elevation of serum L-carnitine on day 3 and significant elevation on day 7 ($p = 0.005$) (Figure 2 and Supplementary Table 1).

On day 0, before treatment began, the mean DE measurement for the entire sample was 13.35 (±4.01) mm and the mean DTf was 35.97% (±4.71%). There was no significant difference between the two groups for either DE ($p = 0.46$) or DTf ($p = 0.87$) (Table 1). Both DE and DTf showed significant elevation on days 3 and 7 in both groups ($p < 0.05$ for all). There was a significant difference between the DE measurements of the low-dose group and the high-dose group on both day 3 ($p = 0.05$) and day 7 ($p = 0.02$). However, there was no significant difference between the mean DTf of the two groups, either on day 3 ($p = 0.57$) or day 7 ($p = 0.13$) (Figure 3 and Supplementary Table 2). Both DE (+r = 0.58; $p < 0.001$) and DTf (+r = 0.61; $p < 0.001$) were positively correlated with serum levels of L-carnitine (Figure 4). Moreover, a linear regression model showed that serum L-carnitine levels prior to treatment independently predicted diaphragmatic function (DE and DTf). This was true for each parameter both with and without adjustment for age and sex ($p < 0.05$ for all). However, high doses of L-carnitine independently influenced the DE only, with ($p = 0.02$) and without ($p = 0.04$) adjustment for age and sex. There were no significant independent effects of high-dose L-carnitine on the DTf in an unadjusted ($p = 0.25$) or adjusted ($p = 0.17$) model (Table 2)

Table 1. Clinical and demographic variables of the patients.

	Total (N = 60)		Low-dose L-carnitine (N = 30)		High-dose L-carnitine (N = 30)		
Variable	Mean or N	SD or %	Mean or N	SD or %	Mean or N	SD or %	*p*-value
Age (yrs.)	55.05	15.35	56.3	15	53.8	15.9	0.52*
Height (cm)	163.50	8.88	163.8	8.14	163.2	9.69	0.79*
Weight (kg)	77.77	13.48	77.4	12.2	78.1	14.9	0.83*
Sex							
female	23	38.33	11	36.67	12	40	0.79†
Male	37	61.67	19	63.33	18	60	
L-carnitine level (nmol/ml)	44.85	11.62	43.7	11.1	46	12.2	0.87*
L-carnitine status							
Deficient	14	23.33	7	23.33	7	23.33	1†
Normal	46	76.67	23	76.67	23	76.67	
Diaphragmatic excursion (mm)	13.35	4.01	12.97	3.25	13.73	4.67	0.46*
Diaphragmatic thickening fraction (%)	35.97	4.71	36.07	4.97	35.87	4.52	0.87*

*Independent t-test. † chi-square test. *p*-value < 0.05 was considered statistically significant.

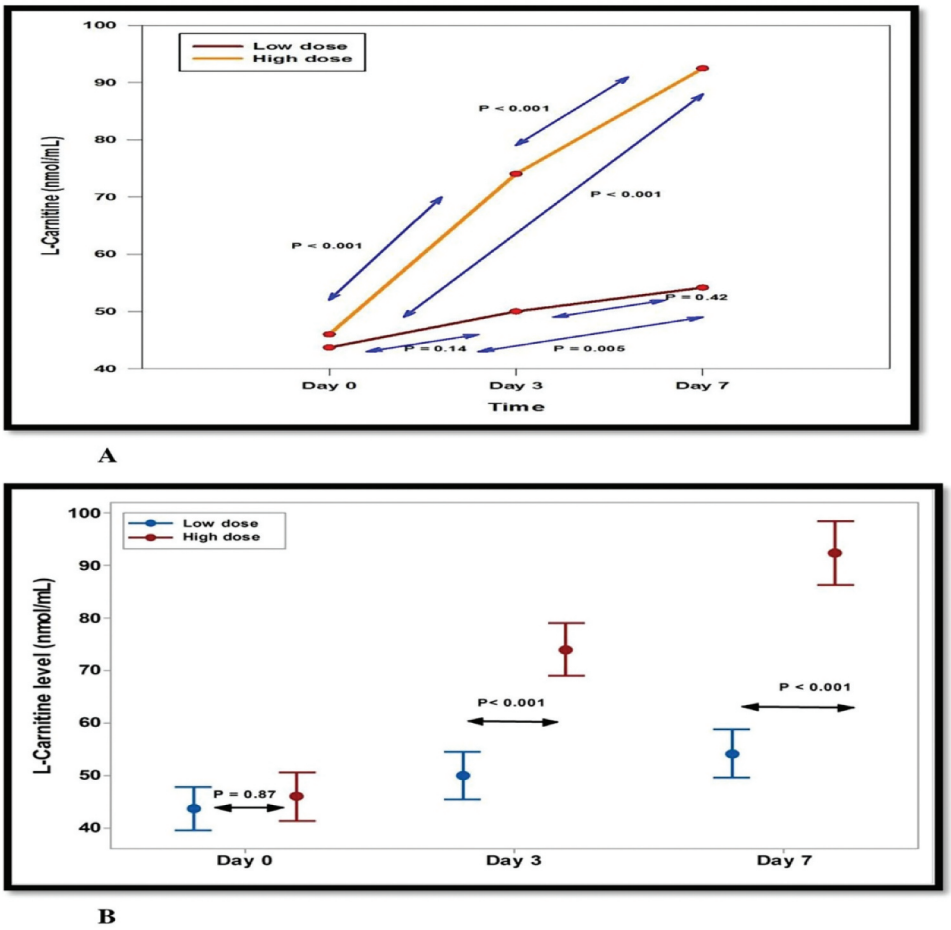

Figure 2. Serum L-carnitine levels in patients with RF after high or low-dose L-carnitine supplementation.
A. Serum L-carnitine levels in both groups at 0, 3, and 7 days. B. Changes in serum L-carnitine levelsfrom day 0 to day 7 in the two groups. The significance of differences in L-carnitine levels between thetwo groups at each time point was determined by one-way ANOVA and Tukey's test. A p-value < 0.05was considered statistically significant.

The lengths of stays in both the ICU and hospital were significantly lower in patients who received high-dose L-carnitine ($p < 0.001$) than those in the low-dose group. Additionally, the length of stay in the ICU was inversely correlated with both diaphragmatic function parameters (DE: −r = −0.51; DTf: −r = −0.41; $p < 0.001$), as were the length of stays in hospital (DE: −r = −0.47; DTf: −r = 0.42; $p < 0.001$) (Supplementary Table 3 and Supplementary Figure 1). The safety of the dosages used was acceptable so adverse effects were limited to a small number of cases of gastrointestinal upset in the form of nausea, vomiting, and/or diarrhea. Patients in both groups complained of these effects and there was no significant difference between the groups in the incidence of nausea ($p = 0.41$), vomiting ($p = 0.32$), or diarrhea ($p = 0.53$) (Supplementary Table 4).

6. Discussion

Although RF is associated with respiratory muscle fatigue, assessing the degree to which a patient is affected by this latter requires medical imaging[9]. Given the debilitating nature of RF, we introduced the use of bedside ultrasound as a means of evaluating the functionality of the diaphragm in RF patients. The measures of DE and DTf attained from ultrasonography reflect the degree of disability and the response to treatment interventions. In this study, we investigated the ability of high-dose and low-dose L-carnitine supplementation to promote diaphragmatic muscle strength and function in RF ICU patients.

The prevalence of L-carnitine deficiency in our cohort, before treatment, was 23.33%, which is consistent with the prevalence found in a 2018 case series[10]. The latter series found that, in undernourished critically ill patients, serum levels of L-carnitine reached 45 (3.58) nmol/L[10]. This was also close to our findings in the present study. However, a higher prevalence of 41% has been reported in pediatric patients[11]. L-carnitine deficiency is less common in adults and older children than in younger children. The main dietary sources of L-carnitine are dairy products, eggs, and meat [12,13]. The administration of high-dose L-carnitine caused a dramatic elevation in serum levels by the third day of treatment ($p < 0.001$) and a significant increase was observed in the low-dose group by day 7 ($p = 0.005$).

The present work has focused on the relevance of diaphragmatic performance to outcomes in patients with RF. The respiratory muscle fatigue known to occur in this patient demographic was reflected in

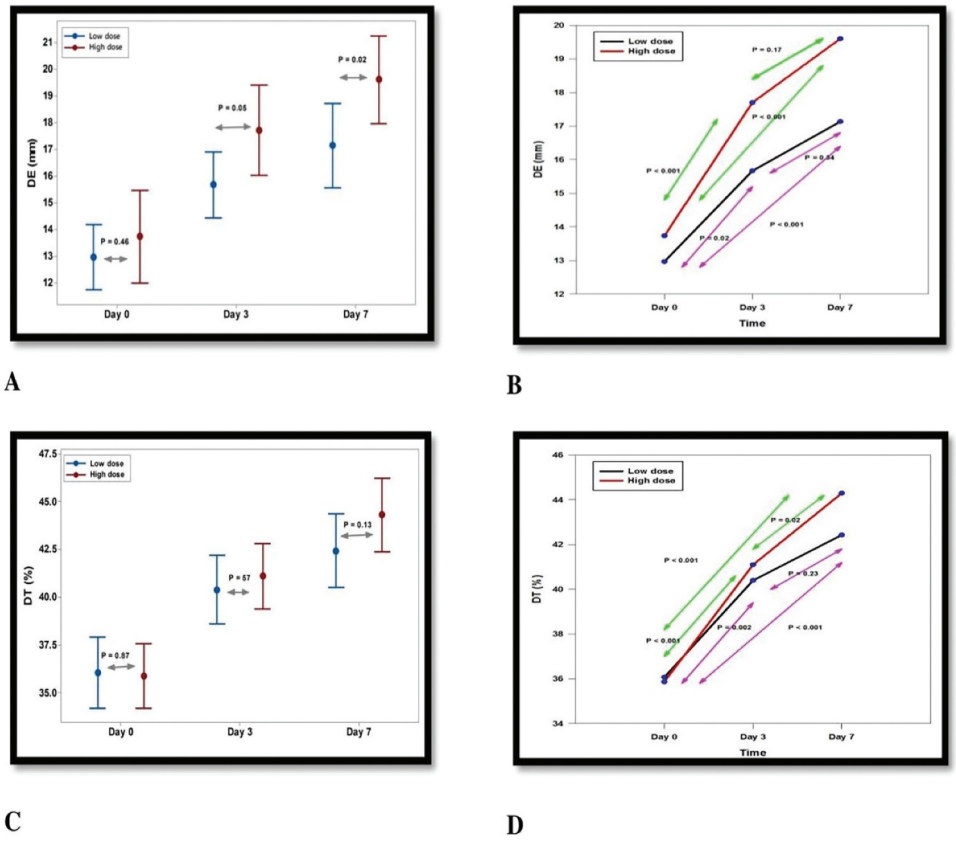

Figure 3. Changes in diaphragmatic function parameters.
A: Differences between diaphragmatic excursion (DE) in each group at days 0, 3, and 7. B: Each group changes in DE from day 0 to day 7. C: Differences in diaphragmatic thickening fraction (DTF) in each group from days 0,3, and 7. D: Changes in DTf from days 0,3, and 7 in each group. Significance was determined by one-way ANOVA with Tukey's post-hoc test. Significance was determined by independent t-tests. A p-value < 0.05 was considered statistically significant.

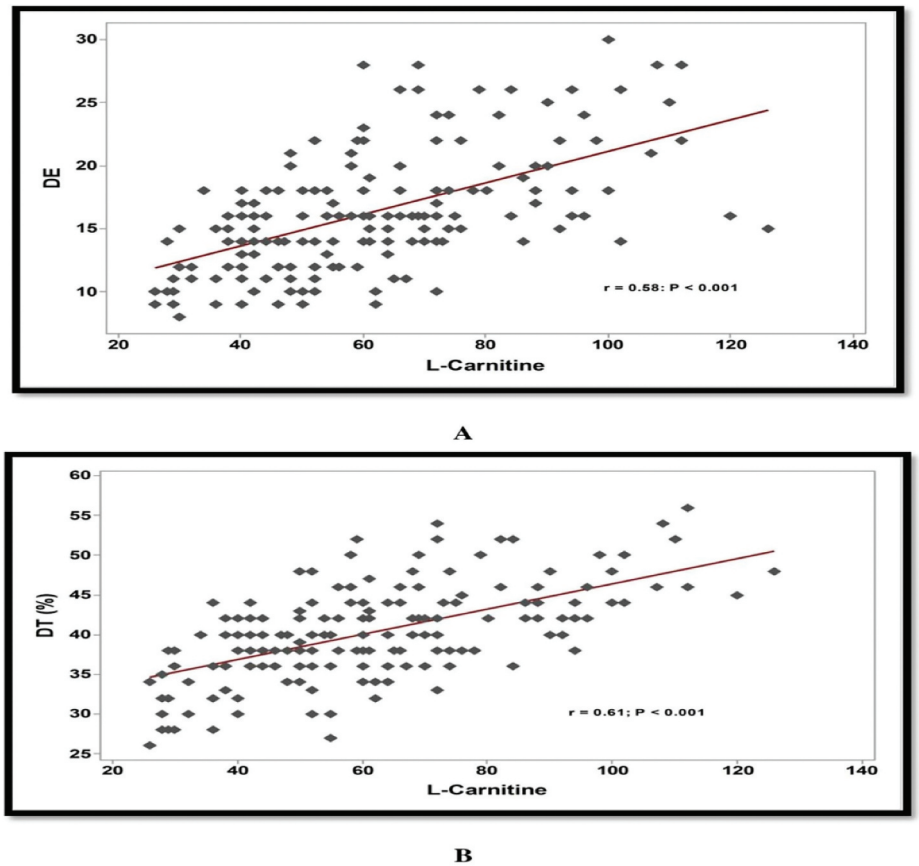

Figure 4. Correlations between serum L-carnitine levels and diaphragmatic parameters.
A. Correlations between L-carnitine and diaphragmatic excursion (DE). B. Correlations between Lcarnitine and diaphragmatic thickening fraction (DTf). The sign before "r" denotes the direction of the relationship. Correlations between L-carnitine and the two diaphragmatic parameters were identified using Pearson's correlation coefficient

Table 2. Effects of L-carnitine on parameters of the diaphragmatic function.

	diaphragmatic excursion		diaphragmatic thickening fraction	
	Coefficient	*p*-value*	Coefficient	*p*-value*
Unadjusted				
L-carnitine level	0.17	< 0.001	0.25	< 0.001
L-carnitine dose (high)	2.1	0.04	1.29	0.25
Adjusted for age and sex				
Age	0.003	0.913	0.015	0.655
Sex (male)	2.718	0.008	2.94	0.01
L-carnitine level	0.155	0.001	0.23	< 0.001
L-carnitine dose (high)	2.208	0.025	1.46	0.175

*Linear regression analysis. *p*-value < 0.05 was considered statistically significant.
The sign before each coefficient value denotes the direction of the relationship.

the pretreatment values obtained in measures of diaphragmatic function. Thus, the mean pretreatment DE for the entire sample was 13.35 (±4.01) mm and the mean DTf was 35.97% (±4.71%). These are significantly below the established healthy value ranges. For DE, the normal range is 11–213 mm; while, for DTf, the normal range is 13%–80% [14,15]. Additionally, both of the diaphragmatic parameters were positively correlated with serum L-carnitine levels and significant increases in both parameters were observed by day 3 of treatment in both groups ($p = 0.02$ and $p < 0.001$; $p = 0.002$ and $p < 0.001$, respectively). High doses of L-carnitine produced significantly greater improvement in DE than low doses on both day 3 ($p = 0.05$) and day 7 ($p = 0.02$). However, there was no significant difference in DT between the high and low-dose groups on day 3 ($p = 0.57$) or day 7 ($p = 0.13$).

L-carnitine plays a crucial role in muscle fatigue reduction[16]. It is responsible for the separation of muscle glycogen and mitochondrial oxygenation of long-chain fatty acids [17,18]. It also improves exercise capacity, especially in muscles with type I fibers such as the diaphragm muscles [19,20]. However, there is a lack of data on the effects of carnitine intake that is high enough to enable copious storage of supplies of L-carnitine in the muscles for future use.

The present study has demonstrated that serum L-carnitine levels can independently predict diaphragmatic mobility ($p < 0.01$). It has also shown that high-dosage L-carnitine treatment can improve DE ($p = 0.04$ and $p = 0.02$) but does not significantly affect DTf, ($p = 0.2$ and $p = 0.17$). This effect on DE might be explained by the ability of L-carnitine to augment blood flow and oxygen supply to muscles through the improvement of endothelial function while reducing any cellular and biochemical disruptions that would result from hypoxia[21]. A study of patients with COPD of varying severity found that L-carnitine supplementation can improve inspiratory muscle performance, strength, and exercise tolerance[22].

We found L-carnitine supplementation to have indirect effects on the outcome of patients with RF by improving diaphragmatic mobility (DE and DT). This led to shorter stays in the ICU and the hospital. This was a dosage-dependent effect, as the larger the dose of L-carnitine supplementation, the shorter the length of stay in both the ICU and the hospital. This finding contrasted with that of a previous study of sepsis patients by Jones et al., who found neither high nor low doses of L-carnitine to have significant effects on the length of stay in the ICU [7]. However, this difference between the two studies can be explained by differences in the patient demographic, since the cellular response to acute and chronic ventilator hypoxia is quite different from that in tissue hypoxia[23].

Nevertheless, there is a shortage of data on the relationship between serum L-carnitine levels, supplementation dosages, and length of stays in ICUs and hospitals. Previous studies have evaluated the effects of L-carnitine supplementation on the long-term mortality of critically ill patients and found a correlation between L-carnitine supplementation dosage and Sequential Organ Failure Assessment scores [7,24,25]. However, a similar study found no significant relationship[26]. A recent systematic review has shown that L-carnitine supplementation can decrease the mortality rate of critically ill patients, especially those with sepsis. The authors of the review encouraged further studies into the optimum dosage and treatment duration[27].

7. Limitations

Our study had some limitations, a small, single-center sample size; this was partially due to the restrictions of our inclusion and exclusion criteria, and the design of the study, in that there was no placebo limb used. Finally, we were unable to attain long-term follow-up data, which could have provided important information on the extent of L-carnitine's effects on respiratory muscle performance.

8. Conclusions

L-carnitine deficiency was observed in less than a quarter of the patients with RF in this study. Serum levels of L-carnitine were positively correlated with measures of diaphragmatic mobility (DE and DT), and

changes in levels were able to independently influence both DE and DTf. Moreover, high-dosage L-carnitine supplementation had rapid significant positive effects on DE. These indirectly improved patient outcomes and led to shorter stays in both the ICU and the hospital. As the supplement has a margin of safety, some minor side effects were reported.

Disclosure statement

No potential conflict of interest was reported by the authors.

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