10.5152/turkjnephrol.2021.4747

Original Article

Turkish Journal of Nephrology

Could L-Carnitine Treatment Have a Protective Role in the Cognitive Function of Patients Undergoing Hemodialysis?

Kadir Gökhan Atılgan[1], Ali Yalçındağ[2], Sibel Örsel[3], Mehmet Deniz Aylı[1]

[1]Department of Nephrology, University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey
[2]Department of Biochemistry, University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey
[3]Department of Psychiatry, University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

Abstract

Objective: This study aimed to assess whether the administration of L-carnitine (LC) was effective on the cognitive function of patients on hemodialysis (HD).
Materials and Methods: Results of 33 patients who received 1000 mg of LC intravenously thrice a week for 6 months and 40 patients who did not receive LC were assessed. The mini-mental state exam (MMSE) was used to assess the cognitive function. An MMSE score of <24 was considered to be a cognitive impairment (CI).
Results: The rate of CI was 42.5% in patients on HD. The MMSE score of patients who had received LC was higher than those who did not (24.79±3.577 and 22.70±5.341, respectively, p=0.046). The MMSE score of men was higher than women (24.74±4.374 and 21.78±4.766, respectively, p=0.009). The MMSE score was significantly lower in patients with diabetes than in those without diabetes (20.69±6.343 and 24.47±3.822, respectively, p=0.004). It was demonstrated in the multiple general linear model analysis that age (p<0.001), sex (p<0.001), diabetes (p=0.010), total carnitine (p=0.005), and free carnitine (p=0.003) were independent factors affecting the MMSE scores.
Conclusion: These findings suggest that regular follow-up of serum carnitine levels and replacement of LC could be positive factors in improving cognitive function in patients on HD.
Keywords: Carnitine, neuropsychological tests, hemodialysis

Corresponding Author: Kadir Gökhan Atılgan ✉ drgokhanatilgan@gmail.com
Received: 13.11.2020 **Accepted:** 03.01.2021

Cite this article as: Atılgan KG, Yalçındağ A, Örsel S, Aylı MD. Could L-Carnitine Treatment Have a Protective Role in the Cognitive Function of Patients Undergoing Hemodialysis?. Turk J Nephrol 2021; 30(1): 77-83.

INTRODUCTION

Cognitive function is a term used to describe thinking skills, including attention, memory, and reasoning (1). Although cognitive decline is less severe in mild cognitive impairment than in dementia, it is a chronic condition, which is the harbinger of dementia in nearly one-third of the affected patients (2). The prevalence of cognitive impairment (CI) is increasing worldwide, and interventions are increasingly becoming more significant. According to a study by the medical research council of the United Kingdom, the prevalence of CI is 18% (3).

Recent studies performed using neuropsychological tests have revealed that the prevalence of CI among patients with end-stage kidney disease is between 16% and 38% (4). It has been reported that this rate is approximately 70% in patients aged ≥55 years who are receiving hemodialysis (HD) treatment (5). A decline in cognitive function influences the prognosis in patients on HD adversely. The patient's treatment compliance, quality of life, and daily life activities are negatively affected by this condition.

Conventional risk factors (such as age, diabetes mellitus [DM], hypertension [HT], atherosclerotic heart and cerebrovascular diseases), and unconventional risk factors, specifically in patients on HD, in CI include anemia, muscle weakness, malnutrition, inflammation, oxidative stress, and intradialytic hypotension (6).

The rapid fluid exchange between blood and dialysate compartments in patients on HD may lead to fluctuations in blood pressures. Increased ultrafiltration rates and

amounts have been associated with decreased cerebral blood flow and impaired cognitive function (7). It has been revealed that intradialytic hypotension is associated with brain atrophy (8).

The use of carnitine, which is associated with energy production by ß oxidation of long-chain fatty acids in mitochondria, in the HD drug treatment scheme was limited to erythropoietin-resistant anemia, muscle weakness, dyslipidemia, intradialytic hypotension, and muscle cramps in the guidelines (9). An animal study, which investigated whether there was the correlation between major depressive disorder and carnitine deficiency, suggested that there were more benefits from carnitine preparations. The decrease in the expression of brain derived neurotrophic factor (BDNF) has been detected in major depressive disorder, and stopping or decreasing glutamate release from synaptosomes are the expected effects of antidepressants (10). This study on mice has revealed that carnitine has a rapid antidepressant effect with synaptic plasticity through acetyl derivative and acetylation of histones, BDNF expression, and synaptic glutamate release regulator metabotropic glutamate receptor class-2 (11-13). The neuroplastic role of carnitine has been highlighted once again by the crucial role it plays in mental and cognitive functions.

Carnitine can be taken naturally through foods rich in protein. It is well-documented that the serum levels of carnitine, which can be synthesized and stored in the body (primarily synthesized in muscle, liver, and kidney), decrease in patients on HD because of the loss of carnitine with HD, lack of renotubular reabsorption, and inadequate intake of essential amino acids that are required for carnitine production. This study aimed to assess whether intravenous (IV) L-carnitine (LC) administration for 6 months had any impact on the cognitive functions of patients on HD.

MATERIALS AND METHODS

Patients and Protocols

This study, for which a case-control design was planned, was performed in the HD unit of our hospital. Patients aged ≥18 years who had not been diagnosed with dementia or depression previously were included. They were administered 4 hours of HD treatment thrice a week for at least 24 months. Patients with a recent surgical intervention, a medical history of malignancy, rheumatologic disease, or mental or physical disabilities were excluded. This study was performed in accordance with the ethical principles of the Helsinki Declaration. Ethical approval for this study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital (Approval Date: February 2, 2018; Approval Number: 55/05). Informed consent was obtained from all the patients included in this study.

A total of 33 patients who received IV 1000 mg of LC per session for 6 months after the HD session constituted the study group, and 40 patients who had no LC treatment constituted the control group. Laboratory results, HD durations, weight at the onset and end of the HD, presence of HT, DM, and coronary artery disease (CAD), and medical history of the patients were obtained from the patient files. Serum total and free LC levels were obtained the day on which the mini-mental state examination (MMSE) was performed, just before the planned HD session. The correlation between the scores of MMSE and age, sex, total carnitine (TC) levels, free carnitine (FC) levels, HT, DM, CAD, HD duration, and interdialytic weight gain (IDWG) were analyzed.

Measurements

Routine biochemistry tests were performed in the central biochemistry laboratory of our hospital.

Serum Carnitine Level Measurements

Serum TC and FC levels were measured through the enzyme-linked immunosorbent assay (ELISA) technique via the Epoch (BioTek Instruments, Inc.; Winooski, VT, USA) microplate spectrophotometer device. Blood samples were taken just before the HD session. The samples were centrifuged for 10 minutes at 3000 revolutions per minute. Serum samples were stored at -20°C. SunRedBio human TC ELISA kit and human FC ELISA kits were used to measure the levels of TC and FC. The results were recorded as µmol/L.

Interdialytic Weight Gain

Interdialytic weight gain (kg) was calculated as predialysis weight minus the postdialysis weight of the previous HD session (14). The average of all 6-month HD sessions was procured to calculate the IDWG.

Mini Mental State Exam (MMSE)

This exam was used for cognitive function assessment because it is easily accessible, most preferred in studies, and allows comparison. The test comprises of time orientation (0-5); place orientation (0-5); speaking 3 words (0-3); attention and calculation; counting backward in 7s (0-5); remembering 3 words (0-3); comprehending the language; performing the task according to 3-step commands; naming, repeating, and writing sentences (0-

Main Points

- The prevalence of cognitive impairment (CI) among patients with end-stage kidney disease is between 16% and 38%. It has been reported that this rate is approximately 70% in patients aged ≥55 years who are receiving hemodialysis (HD).
- A patient's treatment compliance, quality of life, and daily activities are negatively affected by CI.
- In addition to the effects of carnitine on malnutrition, intradialytic hypotension, and dyslipidemia, its effect on synaptic neuroplasticity has also been demonstrated.
- Serum levels of carnitine in patients on HD are lower than those in healthy people.
- The effect of LC on cognitive function in patients on HD is still unknown.

Table 1. Demographic, clinical, and laboratory results of the patients

	Patients on HD who received L-carnitine (n=33)	Patient on HD who did not receive L-carnitine (n=40)	p
Age (year)	55.55±12.06	54.48±13.58	0.870
Sex (female/male)	17 (51.5%)/16 (48.5%)	10 (25%)/30 (75%)	0.020
Total carnitine level (µmol/L)	58.33±9.90	27.23±12.28	0.001
Free carnitine level (µmol/L)	42.75±7.19	18.59±8.07	0.001
Mini-mental state exam score	24.79±3.56	22.70±5.34	0.046
Dialysis duration (month)	70 (48-108)	72 (60-62)	0.257
C-reactive protein (mg/L)	6.96 (3.80-16.40)	12.56 (5.24-21.20)	0.098
Hemoglobin (g/dL)	11.21±1.50	11.51±1.12	0.340
Creatinine (mg/dL)	7.87±1.75	8.31±1.88	0.316
Albumin (g/L)	4.17 (3.7-4.33)	4.22 (4.03-4.49)	0.049
Calcium (mg/dL)	9.16±1.10	8.86±0.70	0.290
Phosphorus (mg/dL)	5.76±1.30	5.10±1.16	0.290
Intact parathormone (pg/mL)	543.90 (406.80-809.50)	432.50 (247.70-601.00)	0.087
Predialysis weight (kg)	69.43±11.91	75.10±14.63	0.082
Postdialysis weight (kg)	67.13±11.84	72.26±14.22	0.108
Interdialytic weight gain (kg)	2.30±0.92	2.84±1.12	0.031
Coronary artery disease	6 (18.2%)	19 (47.5%)	0.009
Hypertension	15 (45.5%)	24 (60%)	0.215
Diabetes mellitus	5 (15.2%)	11 (27.5%)	0.204

HD: hemodialysis

8); drawing a pentagon; and copying (0-1). The MMSE has a total of 30 points, and a score of ≥24 is considered normal, whereas the scores between 23 and 18 as mild-moderate CI, and the score of ≤17 is considered as severe CI (15). The validity and reliability test of the MMSE for the Turkish society was performed previously (16).

Statistical Analysis

The Statistical Package for Social Sciences for Windows, version 25.0, (IBM Corp.; Armonk, NY, USA) was used to analyze data in this study. Descriptive statistics of the obtained data were calculated as the mean±standard deviation or median value, first (25^{th}) and third quartile (75^{th}) (IQR=75^{th}-25^{th}), absolute and relative frequencies, depending on the type and distribution of the characteristics and are summarized in the tables. Groups that received and did not receive LC treatment were compared using the Mann-Whitney U test or independent samples t test, depending on the distribution of numerical features. In addition, the patients who received and did not receive LC treatment were compared regarding the distribution of the categories of categorical features using Fisher's exact test. The compliance of characteristics in numerical type to normal distribution was analyzed using the Kolmogorov-Smirnov test. The effects of the characteristics in numerics on the MMSE score were analyzed using Pearson correlation analysis. Following this stage, the significant features were included in the model together, and their effects on the cognitive function test results were reevaluated using the multiple general linear model. The results were considered statistically significant at $p<0.05$.

RESULTS

A total of 33 (17 women, 16 men) patients undergoing HD who received LC treatment, and 40 (10 women, 30 men) patients undergoing HD who did not receive LC treatment were included in this study. On comparing the groups with and without LC treatment, it was determined that the levels of TC (58.33±9.90 vs 27.23±12.28, p=0.001, respectively), FC (42.75±7.19 vs 18.59±8.07, p=0.001 respectively), and MMSE (24.79±3.56 vs 22.70±5.34, p=0.046 respectively) were significantly higher in those receiving LC treatment. The incidence rates of CAD and IDWG were significantly higher in those who did not receive LC treatment. There was no significant difference between the 2

groups in terms of DM, HT, and laboratory results (p>0.05). The comparative results of the groups that received and did not receive LC treatment are presented in Table 1.

There was a positive correlation between the MMSE score and levels of TC and FC (r=0.386, p=0.001 and r=0.385, p=0.001, respectively). It was determined that there was a significant but negative correlation between age and MMSE score (r=-0.541, p=0.001). No significant correlation was determined between the MMSE score and HD duration or IDWG (p>0.05). The results are presented in Table 2.

Table 2. Evaluation of patients' numerical variables and cognitive function test relationships

	Mini-mental state exam		
	r	**p**	**N**
Total carnitine level	0.386	0.001*	73
Free carnitine level	0.385	0.001*	73
Age	-0.541	0.001*	73
Dialysis duration	0.167	0.159	73
Interdialytic weight gain	0.012	0.923	73

*Pearson correlation analysis

The findings showed that the mean MMSE score of patients on HD who had received LC treatment was higher than in patients on HD who did not receive LC treatment (24.79±3.58 vs 22.70±5.34, p=0.046, respectively). The mean MMSE score of men was determined to be significantly higher than for women (24.74±4.37 vs 21.78±4.77, p=0.009, respectively). It was observed that the MMSE score was significantly lower among patients with DM than in those without DM (20.69±6.34 vs 24.47±3.82, p=0.004, respectively). No significant correlation was found between MMSE scores and patients with or without CAD or HT (p>0.05). The results are presented in Table 3.

The factors (TC, FC, age, sex, and DM) that were statistically determined to have separate effects on the MMSE score were examined in the multiple general linear models. Hence, their effects on the MMSE score could be reevaluated when all the factors were together. Therefore, the findings showed that the levels of serum TC and FC, age, sex, and DM independently had a significant impact on the cognitive function of patients receiving HD (Table 4).

The findings obtained in this study showed that 25 patients aged ≥55 years (7 women and 3 men who received LC treatment, 7 women and 8 men who did not receive LC treatment) and 6 patients younger than 55 years (1 woman who received LC treatment and 2 women and 3 men who did not receive LC

Table 3. Effects of categorical type patient characteristics on cognitive function test

		Mini-mental state exam		
		N	**Mean**	**SD**
L-carnitine treatment	Patients on HD who received L-carnitine	33	24.79	3.58
	Patients on HD who did not receive L-carnitine	40	22.70	5.34
	p=0.046			
Sex	Women	27	21.78	4.77
	Men	46	24.74	4.37
	p=0.009			
Coronary artery disease	No	48	24.13	4.42
	Yes	25	22.72	5.20
	p=0.230			
Hypertension	No	34	22.97	4.84
	Yes	39	24.23	4.59
	p=0.258			
Diabetes mellitus	No	57	24.47	3.82
	Yes	16	20.69	6.34
	p=0.004			

Fisher's exact test
N: patient number; SD: standard deviation; HD: hemodialysis

Table 4. Combined effects of factors on cognitive function test

Variables	p
Sex	<0.001
Diabetes mellitus	0.010
Age	<0.001
Total carnitine	0.005
Free carnitine	0.003
Multiple general linear model	

treatment) had an MMSE score of <24. Thus, there were 31 patients undergoing HD with an MMSE score of <24 in this study. The ratio of patients with an MMSE score of <24 in the LC group was 33.3% (11/33), whereas this rate was 50% (20/40) among the patient group who did not receive LC and 42.5% (31/73) in total. There were 17 patients aged ≥55 years who received LC treatment and 19 patients who did not receive LC treatment. Accordingly, the ratio of patients with an MMSE score of <24 in the group who received LC treatment was 58.8% (10/17), whereas it was 78.9% (15/19) in the group who did not receive LC treatment and 69.4% (25/36) in total. There were 16 patients aged <55 years who received LC, and among 37 patients, 21 who did not receive LC treatment. Accordingly, the ratio of patients with an MMSE score of <24 among the group who received LC treatment was 6.3% (1/16), whereas it was 23.8% (5/21) among the group who did not receive LC treatment and 16.2% (6/37) in total. The ratio of women with an MMSE score of <24 among the LC group was 47.1% (8/17), whereas it was 90% (9/10) among the group who did not receive LC treatment and 63% (17/27) in total. Upon assessing the male patients, the findings showed that the ratio of MMSE score of <24 was 18.8% (3/16), 36.7% (11/30), and 30.4% (14/46) among those who received and who did not receive LC treatment, and in total, respectively. The rate of patients with DM undergoing HD with an MMSE score of <24 was 40% (2/5) among those who received LC treatment, whereas it was 63.6% (7/11) in those who did not receive LC treatment and 56.3% (9/16) in total. The rate of patients without DM undergoing HD with an MMSE score of <24 was 32.1% (9/28) in those who received LC treatment, whereas it was 44.8% (13/29) in those who did not receive LC treatment and 38.6% (22/57) in total.

DISCUSSION

The incidence of CI increases with the aging world population, and this rate ranges between 16% and 38% among patients receiving HD (4). In our study, the incidence rate of CI was determined to be 42.5% among patients undergoing HD who were assessed using a neuropsychological test. This rate was 33% among patients undergoing HD who received LC and 50% in those who did not receive the medication. This rate was 69.4% among patients aged ≥55 years who were included in this study. This rate is similar to the rate in the abovementioned previous study (5). When the female patients were considered, this rate was 63%, and it was 56.3% in those with DM. It has been shown through verifying the factors, including age, sex, DM, serum TC and FC levels through multiple general linear model analysis, that these factors independently have a significant impact on the cognitive function. Previous studies on the assessment of cognitive function in patients on HD were mostly designed to reveal the correlation between serum carnitine deficiency and CI. To our knowledge, our study is the first one in this field because it assesses the long-term (>3 months) use of IV LC, with a large number of patients and a control group consisting of patients on HD.

In studies conducted on neuropsychological tests, given that the number of female patients in the trial group was higher than the control group is considered as a factor that affects the result. In our study, the number of women in the group receiving LC treatment was proportionally and numerically higher than the number of men and the number of women in the other group. The rate of female patients undergoing HD with an MMSE score <24 was 47.1% in patients who received LC medication, whereas it reached 90% in those who do not receive the medication, which is a 2-fold increase. The rates were similar in male patients on HD at 18.8% and 36.7%, respectively, and the difference between the rates was about twice. Therefore, irrespective of sex, the MMSE scores of the group that received LC treatment was higher than those of the group that did not. These results corroborate the independent effect of LC treatment on MMSE score in our study, in which age, sex, and DM are shown to be independent factors on MMSE score as stated in the multiple general linear model analysis.

Evans et al. (17) demonstrated that plasma carnitine levels decreased by 40%, and muscle carnitine levels decreased by 20% in those who received HD for at least 12 months. It has been revealed in recent studies on patients on HD that carnitine deficiency is associated with depression (18). It was put forward in the study, which demonstrated the impact of LC on depression (3 sessions per week of IV 1000 mg LC replacement for 3 months) among patients undergoing HD, that the serum carnitine reached the same level as the level of the control group that comprised healthy individuals (19). It was suggested in the same study that LC replacement provided a significant decrease in the scores of self-rating depression scales. The level of FC is between 40 and 50 µmol/L in healthy individuals, whereas it ranges between 19.2 and 32.4 µmol/L among patients on HD who do not receive the LC treatment (20). In our study, the level of FC was 42.75±7.19 µmol/L in the group that received LC medication, whereas it was 18.59±8.07 µmol/L in the group that did not.

It has been well established that the impaired cognitive function coexists with chronic diseases such as HT, DM, and CAD (21). CI affects the course of the disease adversely. Patients with end-stage kidney disease receiving HD treatment are expected

to be most affected by cognitive decline owing to concomitant diseases and other traditional risk factors. It is crucial to assess and follow-up CI in these patients and to investigate preventive measures.

Our study had a few limitations. Serum carnitine levels were not measured using the tandem mass spectrometry, levels of acyl carnitine (AC) were not revealed, only 1 neuropsychological test was performed, and the MMSE test was selected.

In our study, we examined the serum carnitine levels using the ELISA method, because the cost of measurement by the tandem mass spectrometry technique was remarkably high. In addition, the numbers we intended to investigate in this study would not be reached. We determined, as a result of the previous study, that the serum FC level reached the level of healthy individuals through each session of IV 1000 mg LC replacement, which lasted for 3 months (18). The objective of our study was to reveal whether serum TC and FC levels had an impact on the cognitive function of patients undergoing HD.

Because direct AC measurement can be made only using the tandem mass spectrometry technique (the recommended method) and not by ELISA, we could not demonstrate the AC levels. Because the duration and comprehensibility of other tests were not very suitable for the sociocultural level of our patients, we used a neuropsychological test in our study. Our reasons for choosing MMSE were: it could be completed in a short duration, it was easy to grasp for every educational status, and it was the most preferred neuropsychological test among publications in the literature. Designing and performing multicentered prospective studies with more patients and with >1 test would be valuable in verifying our results.

CONCLUSION

Cognitive dysfunction is considered inevitable in patients undergoing HD owing to risk factors, such as atherosclerosis, inflammation, dyslipidemia, intradialytic hypotension, advanced age, and comorbidity. Thus, frequent follow-up of cognitive function and its rehabilitation is vital. LC support in the prevention and rehabilitation of CI in patients who receive HD is crucial for a solution involving the common pathway of all causes.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of University of Health Sciences Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital (Approval Date: February 2, 2018; Approval Number: 55/05).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.G.A.; Design - K.G.A., A.Y., S.Ö., M.D.A.; Supervision - K.G.A., A.Y., S.Ö., M.D.A.; Resources - K.G.A., A.Y., M.D.A.; Materials - K.G.A., A.Y., S.Ö., M.D.A.; Data Collection and/or Processing - K.G.A., M.D.A.; Analysis and/or Interpretion - K.G.A., A.Y., S.Ö., M.D.A.; Literature Search - K.G.A.; Writing - K.G.A., A.Y., S.Ö., M.D.A.; Critical Review - K.G.A., A.Y., S.Ö., M.D.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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