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Original Paper

The Unexpected Effects of L-Carnitine Supplementation on Lipid Metabolism in Hemodialysis Patients

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Key Words
L-carnitine • Hemodialysis • Lipid status • Blood pressure • Supplementation • Outcome

Abstract
Background/Aims: There is a growing body of evidence that the long-term hemodialysis (HD) treatment leads to disturbances of carnitine homeostasis but the results of L-carnitine supplementation in HD patients have been conflicting. In the present prospective study, we investigated the effectiveness of intravenous L-carnitine in mitigating dialysis-related protein-energy wasting (PEW) based on pre-treatment albumin levels. ***Methods:*** Fifty patients (46% male, mean age 63±18.28 years, HD vintage 37.5 (7-288) months) received 1 g L-carnitine intravenously at the end of every HD session for 12 months. Clinical data were obtained from the medical records and charts. Intradialytic hypotension periods (defined as a decrease of systolic blood pressure by ≥ 20 mmHg) were recorded. Dietary habits were evaluated using a self-administered questionnaire prior to L-carnitine supplementation. Laboratory parameters were measured prior to the supplementation and controlled in 6-months intervals. Anthropometric measurements were performed prior to HD session, including „dry" body weight and height, body mass index (BMI), and body composition analysis using bioimpedance spectroscopy. Malnutrition-inflammation score (MIS) was used as a scoring system representing the severity of PEW and an indicator of general functional capacity. ***Results:*** A significant increase in total cholesterol, predominantly on the account of LDL was found (p=0.005). Simultaneously, HDL decreased (p=0.001) while triglyceride levels remained unchanged. Although the rise in serum prealbumin could be observed, lean tissue index (LTI) decreased and fat tissue index (FTI) increased which resulted in reduction of the LTI/FTI ratio (p=0.002). When divided into two groups according to the pre-treatment albumin values (<35 g/L or ≥35 g/L), patients from the higher albumin group showed significant increase in prealbumin (p=0.005), and improved MIS (p=0.03). Multivariate regression analysis showed that higher FTI after introduction of L-carnitine led to greater hemodynamic stability (OR 1.709, 95% CI 1.006-2.905, p=0.048). As

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there was no differences in HD treatment characteristics, primery kidney disease or residual diuresis we could conclude that positive energy balance (with an increase in prealbumin and FTI) eventually led to better hemodynamic stability. ***Conclusion:*** Our results show significant effects of L-carnitine supplementation on lipid metabolism. Further clinical trials, as well as experimental research are needed to define the role of lipid metabolism in CKD population. Significant benefits of L-carnitine supplementation in patients with better initial serum albumin levels suggest that this therapy should not be restricted to patients with the worst nutritional and overall status.

Introduction

Carnitine is an essential enzyme co-factor in energy metabolism, playing a vital role in β-oxidation of long-chain fatty acids [1, 2]. Given the crucial role it plays, carnitine plasma and tissue concentrations should be maintained relatively constant. Through tubular reabsorption, L-carnitine synthesis and selective short-chain carnitine esters excretion kidney is one of the key elements in preserving this balance [3]. Thus, chronic kidney disease (CKD) leads to significant disturbances of carnitine homeostasis, especially free plasma carnitine levels and carnitine muscle deposits [4]. Dialysis-related carnitine deficiency (defined as predialysis plasma concentration of free carnitine < 40 μmol/L) presents as the overlapping of anemia hyporesponsive to erythropoietin (EPO) therapy, intradialytic hypotension (IDH), cardiovascular (CV) complications and skeletal muscle dysfunction [5]. However, results of L-carnitine supplementation in hemodialysis (HD) patients have been conflicting. Some reports claimed L-carnitine to have a benefitial effect on mitigating EPO hyporesponsiveness, reducing dialysis-related muscle cramping and meliorating serum lipid profile [6-8]. Other studies failed to demonstrate such effects [9, 10].

With its major role as a metabolic intermediate, we hypothesized that L-carnitine supplementation could improve nutritional status in HD patients. The main aim of this prospective study was to evaluate the effectiveness of intravenous L-carnitine in mitigating dialysis-related protein-energy wasting (PEW) based on pretreatment albumin levels.

Materials and Methods

The current study was performed at the dialysis unit in the University hospital centre (UHC) Zagreb. Study was approved by the UHC Zagreb Ethics commitee. Among 121 patients treated at our unit, a total of 50 patients received 1 g L-carnitine (Carnitene Sigma-Tau, Alfasigma Group) intravenously (5 ml of preparation applied slowly within 2-3 minutes) at the end of every HD session for 12 months. Inclusion criteria were as follows: at least 6 months of HD treatment, poor appetite with unintentional weight loss ≥ 5% over 3 months, and signs of PEW with serum albumin levels ≤ 38 g/L and Malnutrition-Inflammation Score (MIS) ≥ 5. Exclusion criteria were uncontrolled and untreated malignant disease, diabetes mellitus and lipid lowering therapy. Clinical data were obtained from the medical records and charts. This included demographic data, underlying kidney disease, HD vintage and treatment characteristics (duration, ultrafiltration (UF) rate, blood flow, Kt/V), EPO therapy and intravenous iron dose, blood pressure (BP) before and after dialysis session as well as residual kidney function (daily urine output > 300 ml). IDH periods (defined as a decrease of systolic blood pressure by ≥ 20 mmHg) were recorded. The following dietary habits were evaluated using a self-administered questionnaire prior to L-carnitine supplementation – number of meals per day, skipping breakfast, skipping intradialytic meal and number of meat products consumated weekly. Appetite was graded 6 and 12 months after the start of supplementation. Laboratory parameters were measured prior to the supplementation and controlled in 6-months intervals. Anthropometric measurements were performed prior to HD session, including „dry" body weight and height, body mass index (BMI), and body composition analysis using bioimpedance spectroscopy (The Fresenius Medical Care Body Composition Monitor – BCM). MIS was used as a scoring system representing the severity of PEW and an indicator of general functional capacity [11].

Statistical analysis

Statistical analysis was performed using Stata/SE 11.2 for Windows (StataCorp LP, USA). Differences between two groups were analyzed by Pearson's χ^2 test, (or Fisher's exact test if any expected cell frequency in contingency table was ≤ 5) for categorical variables, by Student's *t*-test for normally distributed continuous variables and by Wilcoxon test for non-normally distributed continuous variables, at the level of significance $P < 0.05$. Spearman Rank Order Correlations was used to determine correlation between variables.

Results

There were 23 male (46%) and 27 female (54%) patients, mean age 63±18.28 years. The leading cause of CKD was chronic glomerulonephritis (36%), followed by nephroangiosclerosis (18%) and polycystic kidney disease (PKD) (16%). The median time spent on HD was 37.5 (7-288) months, with a minimum treatment time of 3 hours for 2 to 4 times a week, blood flow rate 290.8 (250-350) ml/min and average Kt/V 1.29. Bicarbonate HD and ultrapure dialysate with a flow rate of 500 ml/min was used for all patients, as well as high-flux polysulphone dialysers. Symptomatic IDH occurred in 26% of patients (in 9.79% of dialysis sessons) prior to L-carnitine applications. The primary kidney disease had no influence on neither nutritional parameters nor on L-carnitine supplementation effects. Wilcoxon test revealed that L-carnitine supplementation in our cohort did not influence hemoglobin levels nor led to erythropoetin or intravenous iron dose modifications. There were 8 patients with PKD. Their hemoglobin value was 118 g/L (range 99.8-128.5) before, and 116.5 g/L (range 95.8-137) (p=0.73) after the treatment with L-carnitine, while patients with other primary kidney diseases had hemoglobin levels 109 g/L (range 96-115) before, and 110 g/L (104.5-118) after the treatment with L-carnitine, respectively (p=0.51).

L-carnitine supplementation had pronounced effects on lipid metabolism during the one-year period. Serum concentrations of HDL cholesterol decreased, while LDL cholesterol levels and fat tissue index (FTI) significantly increased. Although prealbumin fraction increased lean tissue index (LTI) fell, thereby leading to decreased LTI/FTI ratio (Table 1).

Table 1. Parameters in both groups according to albumin values prior and after L-carnitine supplementation. *Wilcoxon test

Parameter	Serum albumin < 35 g/L median (interquartile range)		P*	Serum albumin ≥ 35 g/L median (interquartile range)		P*
	Prior (N=12)	After (N=11)		Prior (N=37)	After (N=33)	
Body weight (kg)	70.5 (59 - 81.83)	74 (55 - 89)	0.201	67 (44 - 112)	67 (44 - 112)	0.456
Body height (cm)	171 (159 - 181)	168 (164 - 181)	0.500	167 (153 - 160)	168 (153 - 179)	0.366
BMI (kg/m^2)	24.5 (20.68 - 30)	26.1 (21.86 - 33.09)	0.513	24.35 (17.1 - 35)	24.84 (16.85-33.81)	0.931
Cholesterol (mmol/L)	3.65 (3.15 - 4.68)	3.4 (2.8 - 5.1)	0.648	4 (2.2 - 7.8)	4.1 (2.6 - 8.4)	0.049
Triglycerides (mmol/L)	0.89 (0.08 - 5.13)	1.12 (0.1 - 3.05)	0.112	1.25 (0.52 - 35.13)	1.47 (0.29 - 26.14)	0.226
HDL (mmol/L)	1.17 (0.22 - 1.88)	1.08 (0.67 - 2.08)	0.495	1.07 (0.68 - 2.13)	0.92 (0.6 - 1.9)	0.002
LDL (mmol/L)	1.79 (0.89 - 3.65)	1.87 (0.44 - 3.56)	0.280	2.32 (0.81 - 5.14)	2.54 (1.65 - 5.38)	0.007
Hemoglobin (g/L)	109 (92.5-118.25)	113 (104-119)	0.158	111 (85-150)	108 (91-147)	0.627
Ferritin (μg/L)	190.25 (19.9-833.1)	210.6 (67.7-1025)	0.009	359 (37.5-1141)	412.1 (35.2-1034)	0.133
Iron (μmol/L)	14.5 (7-25)	10 (3-18)	0.139	11 (5-33)	14 (5-27)	0.329
EPO dose (IU/month)	32000 (8000-48000)	48000 (16000-48000)	0.99	32000 (0-72000)	24000 (0-64000)	0.596
IV Fe dose (mg/month)	125 (0-250)	125 (0-250)	0.102	125 (0-400)	122 (0-250)	0.027
Potassium (mmol/L)	4.3 (3.5 - 5.7)	4.9 (3.8 - 6.2)	0.055	5.1 (4.3 - 7.2)	5.3 (3.8 - 6.4)	0.637
Calcium (mmol/L)	2.33 (2.17 - 2.52)	2.28 (2.02 - 2.48)	0.198	2.24 (1.95 - 2.71)	2.26 (1.9 - 2.7)	0.467
Phosphorus (mmol/L)	1.41 (0.72 - 2.13)	1.33 (0.36 - 2.25)	0.363	1.68 (0.74 - 3.07)	1.82 (0.87 - 3.32)	0.047
Total protein (g/L)	63 (51 - 69)	60 (45 - 75)	0.875	66 (56 - 77)	67 (60 - 75)	0.105
Serum albumin (g/L)	34.25 (31 - 35)	33.2 (26.1 - 34.8)	0.280	37.6 (35.2 - 44.2)	38.7 (35.3 - 44.3)	0.338
MIS	11.5 (6 - 16)	11 (8 - 18)	0.899	8 (5 - 13)	6 (2 - 15)	0.030
Prealbumin (g/L)	0.45 (0.3 - 0.7)	0.5 (0.4 - 1.7)	0.055	0.6 (0.4 - 0.8)	0.7 (0.4 - 0.9)	0.005
Overhydration (L)	2.05 (-0.7 - 6.8)	2.1 (0.1 - 5.1)	0.753	2.2 (-2.1 - 6.8)	2.1 (-9 - 5.2)	0.532
LTI (kg/m^2)	11.1 (6.6 - 15.6)	9.5 (5.8 - 14.4)	0.140	12.9 (8.8 - 21.1)	11.25 (6.4 - 15.3)	0.004
FTI (kg/m^2)	12.15 (0.5 - 24)	16.3 (2.7 - 26.2)	0.293	10.65 (4.7 - 23.3)	13 (4.1 - 21.4)	0.001
LTI/FTI ratio	0.93 (0.29 - 28.6)	0.55 (0.22 - 4.52)	0.088	1.27 (0.38 - 3.26)	0.98 (0.34 - 3.32)	0.005

When divided into two groups according to the pre-treatment albumin values (<35 g/L or ≥35 g/L), patients in the low albumin group increased prealbumin from 0.45 to 0.5 g/L (p=0.055) and slightly decreased MIS from 11.5 to 11 (p=0.899) (Fig. 1, A and B). However, patients from the higher albumin group showed significant increase in prealbumin from 0.6 to 0.7 g/L (p=0.005), and improved MIS from 8 to 6 (p=0.03, Fig. 2, A and B). These patients also showed significant improvement in appetite and better functional capacity (Fisher's exact test, p=0.021). The same effects of L-carnitine supplementation were also clearly present after analyzing the patients according to their primary kidney disease (PKD vs. other primary kidney disease, Table 2). Groups did not differ regarding the number of dialysis sessions per week (average 2.92 vs. 2.89, p=0.56), dialysis vintage (median 103.5 (12-110) vs. 98 (7-288) months, p=0.64), Kt/V (mean 1.2±0.33 vs. 1.31±0.22, p=0.62) or residual diuresis (median 750 (0-2000) vs 560 (0-2000) ml, p=0.35) for the albumin <35 g/L or ≥35 g/L group, respectively. There was also no differences in dietary habits among the groups.

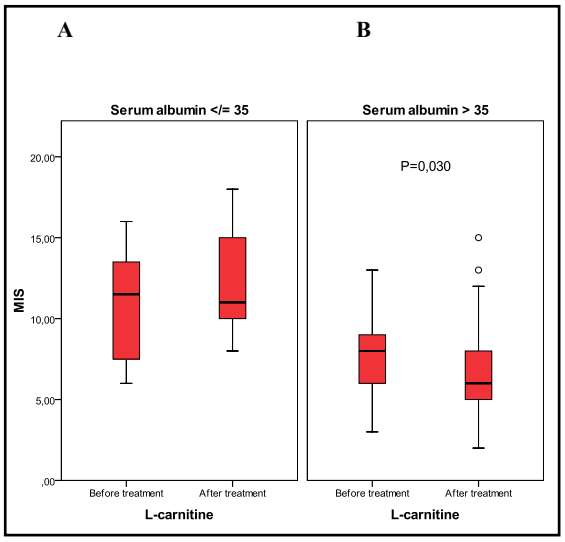

Fig. 1. Changes in Malnutrition-Inflammation Score after L-carnitine supplementation according to pretreatment albumin values.

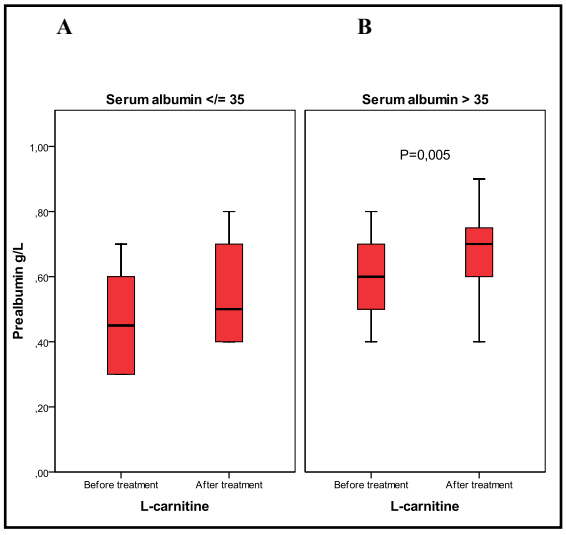

Fig. 2. Changes in prealbumin after L-carnitine supplementation according to pretreatment albumin values.

Before the introduction of L-carnitine, with the increase of BMI, FTI also increased (Rho=0.758, p<0.001), with a reduction of LTI/FTI ratio (Spearman Rho =-0.571, p<0.001, Fig. 3, A and B). After the introduction of L-carnitine, these correlations were more pronounced (Rho 0.770 and -0.582, respectively, p<0.001). Multivariate regression analysis showed that higher FTI after introduction of L-carnitine led to greater hemodynamic stability with number of IDH episodes significantly decreasing during the 12-months period (OR 1.709, 95% CI 1.006-2.905, p=0.048), and appearing in only 8% of patients (in 5.48% of dialysis sessions; Fisher's exact test, p=0.049, Table 3).

L-carnitine treatment had no negative repercussions on dialysis adequacy (average Kt/V was 1.29 before and 1.32 after the treatment with L-carnitine, Fisher's exact test p=0.24), nor were there any adverse events of the treatment.

Table 2. Parameters in groups according to primary kidney disease prior and after L-carnitine supplementation. *Wilcoxon test

Parameter	Polycystic kidney disease (n=8) median (interquartile range)		P*	Other primary diseases (n=42) median (interquartile range)		P*
	Prior	After		Prior	After	
Body weight (kg)	59.2 (53 – 69.6)	62.5 (54.1 – 67.3)	0.6	69.7 (57 – 81.5)	70 (54.5 - 84)	0.46
Body height (cm)	160 (160 - 170)	170 (160 – 159.8)	0.14	170 (160 - 180)	170 (160 - 170)	0.12
BMI (kg/m^2)	22.8 (21.3 – 26.3)	26.1 (21.86 - 33.09)	0.513	24.8 (17.1 - 35)	24.9 (20.6-28.8)	0.35
Cholesterol (mmol/L)	4.2 (3.6 – 5.3)	4.7 (3.6 - 5.4)	0.36	3.9 (3.25 – 4.7)	4.1 (3.4 – 5.1)	0.17
Triglycerides (mmol/L)	1.1 (0.9 - 1.5)	1.7 (1.2 - 2.2)	0.02	1.25 (0.52 - 35.13)	1.47 (0.29 - 26.14)	0.04
HDL (mmol/L)	1.3 (1.1 - 1.3)	1.1 (0.8 – 1.2)	0.02	1.1 (0.9 – 1.3)	1.0 (0.8 - 1.3)	0.02
LDL (mmol/L)	2.5 (1.8 - 3.3)	2.7 (2 – 3.4)	0.4	2.0 (1.6 – 2.9)	2.3 (1.9 – 3.1)	0.008
Hemoglobin (g/L)	118 (99.8 – 128.5)	116.5 (95.8-137)	0.73	109 (96-115)	110 (104.5 - 118)	0.51
Iron (µmol/L)	9.5 (8 – 11.8)	14 (10.5 – 17.3)	0.5	11 (8 - 16)	11 (8.5 - 16)	0.37
EPO dose (IU/month)	20000 (6000-24000)	24000 (0-36000)	0.66	32000 (0-72000)	24000 (0-64000)	0.596
IV Fe dose (mg/month)	187.5 (32.8 - 250)	125 (0 - 250)	0.18	125 (93.8-250)	125 (31.3-162.5)	0.14
Total protein (g/L)	66 (63.3 – 72.3)	67.5 (64.3 – 73.5)	>0.99	65 (62 - 68)	66 (62 – 68.75)	0.18
Serum albumin (g/L)	37.1 (36.1 – 39.9)	37.1 (35.4 – 41.2)	0.46	37 (34.9 - 39)	37.6 (34.5 - 40.2)	0.94
MIS	7.5 (6 – 8.8)	6 (5 – 9.5)	0.010	9 (6.8 - 11)	8 (6 – 10.3)	0.049
Prealbumin (g/L)	0.6 (0.6 - 0.7)	0.7 (0.5 – 0.8)	0.02	0.6 (0.5 - 0.7)	0.7 (0.5 - 0.7)	0.003
Overhydration (L)	1.8 (0.1 - 4.8)	1.6 (0 - 3.1)	0.14	2 (0.9 – 3.7)	2.3 (0.9 - 4)	0.67
LTI (kg/m^2)	11.6 (10.6 - 14)	9.4 (7.2 - 11.9)	0.01	12.5 (10.1 – 13.9)	11.2 (9.9 – 12.9)	0.04
FTI (kg/m^2)	10.4 (8 – 13.1)	14.8 (10 - 18)	0.02	10.8 (7.7 – 15.2)	13 (8.1 – 16.9)	0.03
LTI/FTI ratio	1.3 (0.9 – 1.5)	0.8 (0.4 - 1)	0.01	1.2 (0.8 – 1.8)	0.9 (0.6 – 1.5)	0.02

Fig. 3. Changes in LTI/FTI ratio after L-carnitine supplementation according to pretreatment albumin values.

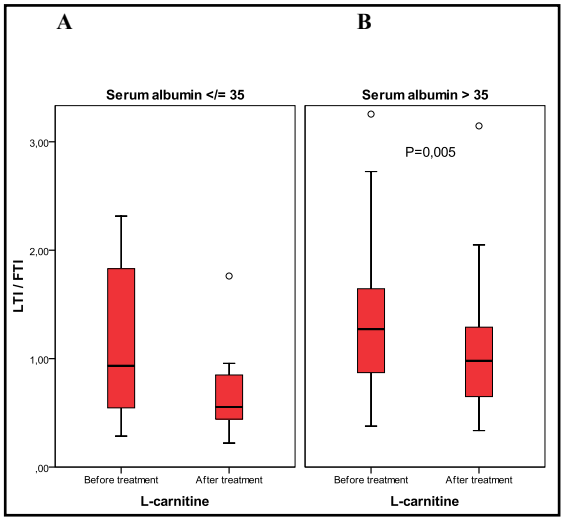

Table 3. Distibution of patients with and without hypotension prior and after L-carnitine supplementation. * Fisher's exact test

Parameter		Number (%) of patients prior to L-carnitine supplementation			P*
		Without hypotension	With hypotension	Total	
After L-carnitine supplementation	Without hypotension	36 (97)	10 (77)	46 (92)	0.049
	With hypotension	1 (3)	3 (23)	4 (8)	
	Total	37 (100)	13 (100)	50 (100)	

Discussion

Our results demonstrated marked effects of intravenous L-carnitine supplementation on lipid metabolism. A significant increase in total cholesterol, predominantly on the account of LDL was found. Simultaneously, HDL decreased while triglyceride levels remained unchanged. Although the rise in serum prealbumin could be observed, LTI decreased and FTI increased which resulted in reduction of the LTI/FTI ratio. Alhough at first these changes appear as negative, they were associated with improved hemodynamic stability, MIS and appetite, and were more pronounced in patients with better initial albumin levels.

Our study showed that 12 months of intravenous L-carnitine supplementation had no impact on hemoglobin levels nor did it lead to a reduction in EPO requirement. This finding is in accordance with Handelman's study from 2006 which showed that 6 months of L-carnitine administration to patients in a large dialysis unit did not change hemoglobin or EPO dose [12]. Meta-analysis by Hurot et al. suggested a beneficial effect of L-carnitine supplement on anaemia control in HD patients with reducing the EPO resistance index and improving EPO efficiency as compared with control groups. They were not able to find dose-response pattern, and did not observe a time gap for this effect [13]. Due to small number of studies and limited number of patients Chen et al. recently conducted another meta-analysis which failed to confirm those findings [8].

According to our results, L-carnitine supplementation significantly decreased number of IDH episodes (OR 1.709, 95% CI 1.006-2.905, p=0.048), complicating only 5.48% of dialysis sessions; Fisher's exact test, p=0.049). IDH is a common complication of HD which could lead to premature treatment discontinuation, chronic underdialysis and higher mortality. It is mainly linked to poor compensatory response to ultrafiltration, with autonomic or baroreceptor failure or disturbed cardiac function leading to excessive venous pooling and abnormal vasodilation [14]. New evidence also suggests that mitochondria dysfunction might have a primary role in the development of CKD related complications. This results in mitochondria-derived oxidative stress and leads to persistent tissue damage. As L-carnitine is an essential enzyme co-factor in energy metabolism it could be one of the so called mitochondria-targeted molecules which could modulate the specific signal transduction cascade and lead to significant improvement of cellular defense against chronic inflammation and oxidative stress [15]. Moreover, after performing multivariate regression analysis we were able to show a link between the FTI increase and a lesser number of IDH episodes which could suggest that positive energy balance (with an increase in prealbumin and FTI) and a reduction of MIS eventually led to better hemodynamic stability.

The relationship between L-carnitine therapy and lipid metabolism has been widely investigated but with conflicting results. Our data are in contrast with previously published studies which described either beneficial effects or no changes at all. By beneficial effects authors have stressed a significant decline in triglycerides, free fatty acids and cholesterol levels (total and LDL fraction) and an increase in HDL [16-19]. On the other hand, results obtained by two systematic reviews and meta-analysis provided no evidence that L-carnitine could impact lipid metabolism [13, 20]. These differences could possibly be explained by the dose-dependent effects of carnitine proposed by some reports [8, 21].

Cardiovascular (CV) complications are the leading cause of mortality in HD patients, with accelerated atherosclerosis and PEW being among the most important risk factors leading to poor outcome [22]. Although obesity, hypercholesterolemia and higher BP values are well-established risk factors for CV disease and poor outcome in general population, it seems that higher rather than lower values for these risk factors act protective in CKD patients [23-26]. This phenomenon is called „reverse epidemiology" or „dialysis-risk-paradox" [23, 26, 27]. Several possible mechanisms explaining favorable effect of higher BMI on survival have been proposed so far. All hypothetical explantations lead to one particular point – adipose tissue does not serve only as lipid storage but is also a highly active endocrine organ [28, 29]. As PEW is defined not only by the continuous decline in protein but also fat reserves, its treatment represents a challenge and should be focused on maintaining the energy pool as whole.

Even though our results are contradictory to previously published studies [13, 16-20], one could speculate whether this slight but significant increase in total and LDL cholesterol and FTI could in fact be protective in HD patients. Although at first these changes could be claimed as undesirable they led to significant amelioration of MIS and were linked to much better appetite. Furthermore, FTI increase led to lesser number of IDH episodes. As there was no differences in HD treatment characteristics, primery kidney disease or residual diuresis we could conclude that positive energy balance (with an increase in prealbumin

and FTI) eventually led to better hemodynamic stability. This hypothesis deserves further investigations. Although L-carnitine treatment had no negative repercussions on Kt/V indeces, dialysis adequacy parameters should be carefully monitored.

Our study has some limitations including the small sample size, lack of control group, limited laboratory lipid-metabolism evaluation and short follow-up. When evaluating dietary habits by using a self-administered questionnaire prior to L-carnitine supplementation there was no differences between these two groups. However, more detailed food intake analysis was not performed. Thus, there is a possibility that the former group did not have the same dietary habits as the other analyzed group. Although this may be the potential source of a bias, patients from the higher albumin group clearly stated improvements in appetite and functional capacity that in our oppinion led to better serum prealbumin and a decrease in MIS. This was also mirrored through the changes in serum lipid profile and phosporus levels.

Additionally, comparing both pre- and postdialysis body composition measurements as well as more detailed food intake analysis might be useful in further studies. Further clinical trials, as well as experimental research are needed to define the role of lipid metabolism in CKD population.

Conclusion

The results of our study showed significant effects of L-carnitine supplementation on lipid metabolism. Significance of increase in the FTI remains unclear, although it may be the consequence of increase in the“healthy“ and protective fat tissue. Due to significant benefits of L-carnitine supplementation in patients with better initial serum albumin levels, this therapy should not be restricted to patients with the worst nutritional and overall status.

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Disclosure Statement

The authors declare no conflicts of interest regarding the publication of this paper.

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