L-Carnitine Treatment in Incident Hemodialysis Patients: The Multicenter, Randomized, Double-Blinded, Placebo-Controlled CARNIDIAL trial

Lucile Mercadal, Mathieu Coudert,† Anne Vassault,‡ Laurence Pieroni,§ Alain Debure,‖ Messaoud Ouziala,‖ Hélène Depreneuf,¶ Christine Fumeron,¶ Aude Servais,** Nader Bassilios,†† Jacques Bécart,†† Ubald Assogba,‡‡ Mahmoud Allouache,§§ Boussad Bouali,§§ Nhan Luong,§§ Marie Paul Dousseaux,* Sophie Tezenas-du Montcel,† and Gilbert Deray**

*Nephrology Department, †Biostatistics Depatment, and §Biology Department, Assistance Publique Hôpitaux de Paris, Pitié Salpétrière Hospital, Paris, France; ‡Biology Department and **Nephrology Department, Assistance Publique Hôpitaux de Paris, Necker Hospital, Paris, France; ‖CMC Pantin, Aubervilliers, Paris, France; ¶Association pour l'Utilisation du Rein Artificiel, Paris, France; ††Clinique de Turin, Paris, France; ‡‡Clinique des Mousseaux, Evry, France; and §§Institut Mutualiste Montsouris, Paris, France

Correspondence: Dr. Lucile Mercadal, Nephrology Department, Pitié Salpétrière Hospital, 41-83 bd de l'hôpital, 75013 Paris, France. Email: lucile.mercadal@psl.aphpfr

Summary

Background L-carnitine levels decrease rapidly and steadily with duration of hemodialysis, and carnitine depletion can impair response to recombinant human erythropoietin (rHuEPO). The study hypothesis was that L-carnitine supplementation during the first year of hemodialysis would improve this response.

Design, setting, participants, & measurements From October 2006 through March 2010, this multicenter, randomized, double-blinded study assigned 92 incident hemodialysis patients to receive placebo or 1 g of intravenous L-carnitine after each dialysis session for 1 year. The primary outcome measure compared the groups for rHuEPO resistance index (EPO-RI), defined as weekly rHuEPO doses (IU/kg body weight divided by hemoglobin level) (g/dl).

Results In the L-carnitine group, carnitine concentration increased from a mean ± SD of 79±51 μmol/L to 258±137 μmol/L; in the placebo group, it declined from 68±25 μmol/L to 53±24 μmol/L (interaction group × time, $P<0.001$). Carnitine deficiency affected about 30% of the patients in the placebo group during the study period. EPO-RI varied from 15.8±11.3 to 9.5±5.8 IU/kg per g/dl in the placebo group and from 20.6±12.8 to 15.6±15.9 IU/kg per g/dl in the L-carnitine group, for a mean variation of −3.94±12.5 IU/kg per g/dl and −2.98±15.5 IU/kg per g/dl, respectively ($P=0.7$). After adjustment for baseline characteristics, the EPO-RI course was similar in each group (difference between groups, $P=0.10$; interaction group × time, $P=0.9$).

Conclusions Carnitine levels decrease by about 11%±33% during the first year of hemodialysis. Treatment of incident hemodialysis patients with L-carnitine does not improve their response to rHuEPO.

Clin J Am Soc Nephrol 7: 1836–1842, 2012. doi: 10.2215/CJN.12431211

Introduction

Carnitine is a hydrophilic amino acid that acts as a cofactor of long fatty-acid metabolism and has an indirect role in glucose metabolism. This small molecule (162 D) is freely filtered by the glomerular membrane and reabsorbed by the proximal tubule *via* organic cation carnitine transporter 2 receptors, with a renal clearance of about 1–3 ml/min. In contrast, hemodialysis commonly clears carnitine at about 100 ml/min (1). Plasma carnitine levels decrease, on average, by about 80% at the end of a dialysis session (2). This plasma depletion is restored after the session, from cellular storage, endogenous synthesis, and food intake. However, endogenous synthesis is altered by the dialysis of cofactors of carnitine synthesis, including vitamin B6, niacin, vitamin C, lysine, and methionine, and by protein malnutrition. Consequently, carnitine depletion develops rapidly after the start of hemodialysis and increases with duration of dialysis (3–6). Additionally, free carnitine is dialyzed at a higher rate than is acyl-carnitine, and carnitine/acyl-carnitine translocase activity may decrease. Both mechanisms tend to invert the plasma acyl/free carnitine level, which can exceed 0.4 (7).

Several carnitine effects might influence response to recombinant human erythropoietin (rHuEPO). Carnitine participates in the deacylation and reacylation processes that remodel erythrocyte phospholipid membranes, stimulates erythropoiesis at high concentrations (>200 μmol/L), increases the survival time of erythrocytes, and reduces oxidative stress *via* heme oxygenase 1 and inflammation (8–14). Observational studies initially described an inverse correlation between rHuEPO dose and carnitine level (15,16). Randomized, controlled studies and a meta-analysis suggested that L-carnitine supplementation might have a positive effect on response to EPO in long-term hemodialysis patients (17–21). Each of these studies included around 30 patients or fewer, highly selected for probable rHuEPO resistance secondary

to carnitine deficiency, defined by a free carnitine level <30 μmol/L (or total <40 μmol/L) (22). These results led to the recommendation of L-carnitine treatment in hemodialysis patients for symptoms potentially related to carnitine deficiency, such as hyporesponsive rHuEPO-dependent anemia (23). The evidence supporting these recommendations is weak, however, and the pediatric recommendation stipulates that there is currently insufficient evidence to suggest a role for carnitine therapy in children with CKD stage 5D (24).

Our hypothesis was that early, prophylactic L-carnitine supplementation could prevent carnitine deficiency, improve rHuEPO responsiveness, and so minimize the need to increase rHuEPO doses.

Materials and Methods

Patients were eligible if they had started long-term hemodialysis <6 months before the study started or afterward and were older than age 18 years. Exclusion criteria were pregnancy, cancer, expected life expectancy <6 months, and documented carnitine deficiency. After providing written informed consent, eligible patients were randomly assigned in a 1:1 ratio with a centralized randomization list stratified according to center. Patients were assigned to receive 1 g intravenous L-carnitine at the end of each dialysis session or double-blinded placebo treatment for 1 year after randomization. Monthly patient monitoring included treatment, clinical events, red blood cell transfusion, dialysis sessions with symptomatic intradialytic hypotension (necessitating a stop to ultrafiltration, the Trendelenburg position, or saline infusion), and midweek predialysis laboratory tests. Additionally, patients had centralized measures of total carnitine, free carnitine, and serum albumin measured by nephelometric methods every 3 months and a lipid profile every 6 months. Forty-one patients completed a dietary questionnaire, and 66 the Short Form-36 (SF-36) questionnaire; 30 of the latter also completed the SF-36 at study end.

This trial named CARNIDIAL was funded by the Ministry of Health. Patients were enrolled from October 2006 through March 2010. Sigma-Tau provided L-carnitine and placebo without charge. The study was approved by the Paris public hospital agency (Assistance Publique Hôpitaux de Paris) ethics committee (NCT 00322322).

Outcomes

The primary outcome measure was whether the change in the rHuEPO resistance index (EPO-RI) during the study period differed between the placebo and the L-carnitine groups. EPO-RI was defined as the mean weekly rHuEPO dose (calculated from monthly dose IU per kg body weight) divided by hemoglobin (g/dl).

Secondary outcomes included the percentages of patients with resistance to rHuEPO (doses >300 IU/kg per week), with red blood cell transfusion, and with dialysis sessions complicated by symptomatic hypotension; total and free carnitine levels; lipid profiles; and physical and mental status, as evaluated by the SF-36 questionnaire.

Statistical Analyses

We estimated that with a total of 110 patients (55 in each group), the study would have 90% power to detect a 30% reduction in the EPO-RI, assuming a 1-year increase of 5% in the placebo group, an annual dropout rate of 30%, and use of a mixed linear model of repeated data with a two-sided α level of 0.05.

Patients' characteristics were described at baseline and compared between groups with the t test for normal quantitative variables, the Mann-Whitney test for non-Gaussian quantitative variables, and Fisher exact test or chi-squared test for qualitative variables. The variation of the EPO-RI during the 1-year study period was compared between groups with a mixed linear model, with the treatment effect characterized by a group × time interaction and the time effect assumed to be linear. A pattern-mixture model was fitted to verify that withdrawals and dropouts did not affect the results. Box-Cox transformation of EPO-RI was used to comply with the conditions of the model's validity (normality and homogeneous variability of residuals). A mixed linear model of EPO-RI was adjusted for determinant factors at baseline, including hemoglobin, EPO doses, transferrin saturation, serum albumin, and nutritional supplement.

Protocol deviation: Only one patient in the L-carnitine group had a temporary stop (<3 months) and was therefore analyzed with the noncompleters (n=11). Statistical analyses were conducted in intention-to-treat and per protocol analyses.

Results

Study Population

The study included 92 patients who began long-term hemodialysis within 39±27 days of randomization, 46 in each group (Figure 1): 84 began hemodialysis for the first time, 1 patient previously had peritoneal dialysis, and 7 had renal transplantations. The baseline characteristics of the two groups differed for rHuEPO doses, serum albumin, C-reactive protein, and total serum calcium but not corrected serum calcium (Table 1).

Primary Outcome

EPO-RI steadily improved in both groups: from 15.8±11.3 at baseline to 9.5±5.8 IU/kg per g/dl at month 12 in the placebo group and from 20.6±12.8 to 15.6±15.9 IU/kg per g/dl in the L-carnitine group (Figure 2), with a mean variation of −3.94±12.5 IU/kg per g/dl in the placebo group, not significantly different from the −2.98±15.5 IU/kg per g/dl in the L-carnitine group (P=0.7). After adjustment for determinant factors at baseline, EPO-RI was similar in both groups (P=0.10), and its course during the study period was similar for each (interaction group × time, β = 0.019±0.17; P=0.8). The results were unchanged in the per protocol analysis and remained similar in sensitivity analyses with subgroups that separately took into account C-reactive protein, serum albumin, iron indices, carnitine level, resistance to rHuEPO, and calorie supply.

Secondary Outcomes

Seven patients in the placebo group (17%; 95% confidence interval [CI], 7%–32%) showed resistance to rHuEPO, compared with 6 (15%; 95% CI, 6%–31%) in the carnitine group (P=0.8). During the study period, the percentage of

Figure 1. | **Flow chart**. Distribution of patients from randomization to completion of the study period.

Table 1. Baseline characteristics

Characteristic	Placebo (*n*=46)	L-Carnitine (*n*=46)	*P* Value
Age (yr)	61±15	61±18	0.9
Weight (kg)	70±13	68±14	0.5
Duration of dialysis (d)	40±29	38±25	0.8
First hemodialysis, *n* (%)	44 (96)	40 (86)	0.2
Prior renal transplantation, *n* (%)	2 (4)	5 (10)	0.4
Vascular nephropathy, *n* (%)	21 (45)	17 (36)	0.4
Glomerulopathy, *n* (%)	10 (21)	11 (24)	0.8
Diabetes, *n* (%)	22 (47)	17 (37)	0.3
Hypertension, *n* (%)	42 (91)	45 (97)	0.3
Converting enzyme inhibitor, *n* (%)	18 (39)	21 (45)	0.5
Nutritional supplement, *n* (%)	5 (10)	6 (13)	1.0
Intravenous iron, *n* (%)	41 (89)	35 (78)	0.14
Weekly intravenous iron (mg)	117±53	116±62	0.6
Weekly rHuEPO dose (IU)	11 931±8 591	13 761±7 415	0.03
EPO- RI (IU/kg per g/dl)	15.8±11.3	20.6±12.8	0.03
Subcutaneous rHuEPO, *n* (%)	16 (36)	15 (33)	0.8
Intravenous rHuEPO, *n* (%)	29 (64)	30 (67)	
Hemoglobin (g/dl)	10.9±1.5	10.4±1.4	0.12
Mean corpuscular volume (fl)	90±6	89±6	0.6
C-reactive protein (mg/L)	12±34	18±40	0.03
Serum albumin (g/L)	35±4	32±7	0.03
Ferritinemia (ng/ml)	164±103	228±225	0.7
Transferrin saturation (%)	23±11	22±14	0.8
Serum calcium (mmol/L)	2.19±0.2	2.09±0.2	0.02
Corrected serum calcium (mmol/L)	2.31±0.2	2.26±0.3	0.4
Total carnitine (μmol/L)	68.2±24.6	78.6±51	0.5
Free carnitine (μmol/L)	52.9±19.6	57.4±30.2	0.6
Calories (kcal/d)	1 687±407	1 696±527	0.6
Protein intake (g/d)	70±21	71±23	0.9
SF-36: Physical Component Summary	27±2	26±2	0.4
SF-36: Mental Component Summary	17±1	17±2	0.5

Values expressed with a plus/minus sign are the mean ± SD. The *t* test or Mann-Whitney test was used for quantitative variables; the Fisher exact test or chi-squared test was used for qualitative variables. rHuEPO, recombinant human erythropoietin; EPO-RI, rHuEPO resistance index calculated as mean weekly rHuEPO doses (IU) per kg body weight divided by hemoglobin (g/dl); SF-36, Short-Form 36.

rHuEPO-resistant patients varied from 6.6% to 0% in the placebo group and 2.2% to 0% in the L-carnitine group. In each group, carnitine levels were similar regardless of rHuEPO resistance. Four patients in the placebo group and 6 in the L-carnitine group received a transfusion of red blood cells during the study period (P=0.8).

Total and free carnitine levels were similar between groups at inclusion. Total plasma carnitine levels rose from

79±51 at baseline to 258±137 μmol/L at month 12 in the L-carnitine group but fell from 68±25 to 53±24 μmol/L in the placebo group (*i.e.*, a mean decrease from month 12 to month 0/month 0 of 11%±33% in the placebo group and a mean increase of 265%±283% in the L-carnitine level; interaction group × time, $P<0.001$; Figure 3A). In the L-carnitine group, the total carnitine level increased by 178% ±219% as early as month 3 (interaction group×month 3, $P<0.001$) and then stabilized (Figure 3A). Conversely, in the placebo group, carnitine level bottomed out at month 6 and then stabilized (Figure 3A). The frequency of carnitine deficiency (free carnitine < 30 μmol/L) was similar in both groups at baseline (placebo group, 12.2% [95% CI, 4%–26%]; treatment group, 12% [95% CI, 4%–27%]); in the placebo group, it reached 29% (95% CI, 14%–48%) at months 3 and 6 and 30% at months 9 and 12 (95% CI, 14%–51%). In the placebo group, 49% of the patients (95% CI, 33%–64%) had a free carnitine level < 30 μmol/L at least once.

The ratio of free to total carnitine was similar in both groups and did not vary significantly during the study period (0.78±0.09–0.77±0.09 in the placebo group; 0.76±0.10–0.73±0.08 in the L-carnitine group) (Figure 3B). Total, HDL, and LDL cholesterol and triglycerides varied similarly in both groups (Figure 4). The percentage of patients with symptomatic intradialytic hypotension

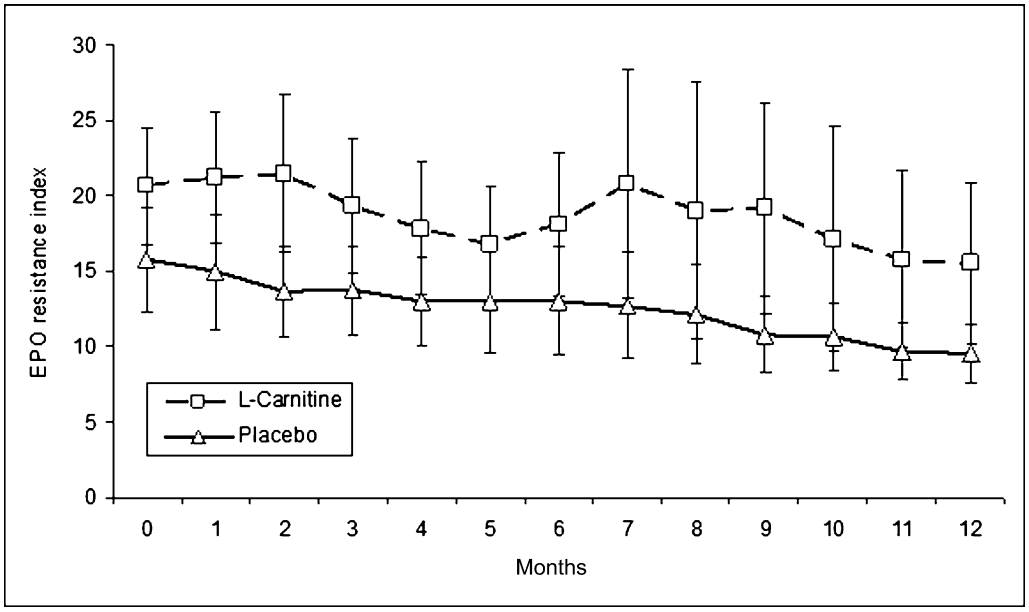

Figure 2. | **Erythropoietin (EPO) resistance index in the placebo and the L-carnitine treatment groups.** Error bars represent 95% confidence intervals. Calculated as mean weekly recombinant human erythropoietin doses (IU per kg body weight) divided by hemoglobin (g/dl) in the L-carnitine and the placebo groups.

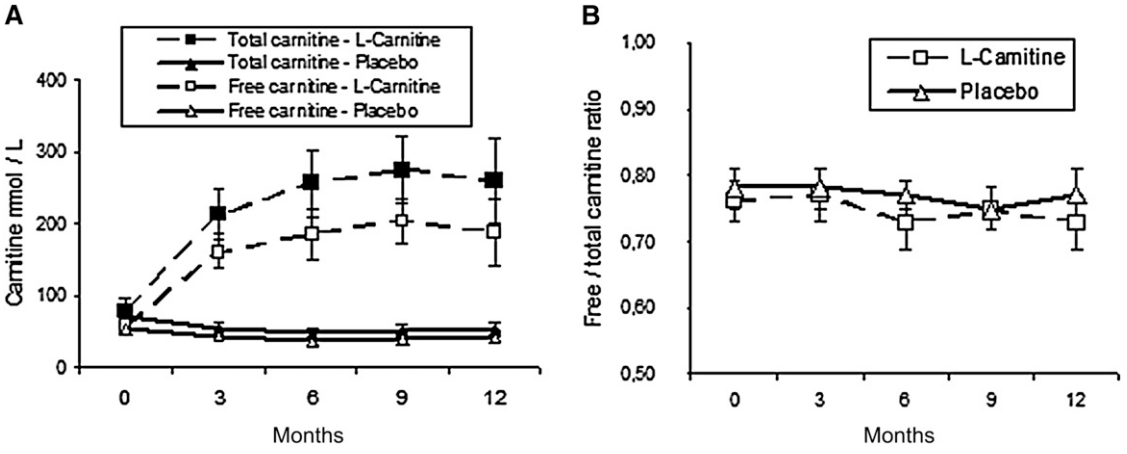

Figure 3. | **Carnitine values in the placebo and L-carnitine groups.** (A) Total and free carnitine levels. (B) Free-to-total carnitine ratios. Error bars represent 95% confidence intervals.

peaked during months 1 and 2 and did not differ between groups (data not shown). The physical status score, as assessed by the SF-36 questionnaire, did not change significantly in either group, increasing in both groups from 26±2 at baseline to 27±2 at month 12.

Adverse Events

We observed 215 adverse events among 50 patients (54.35%): 94 events among 22 patients in the placebo group and 121 among 28 in the L-carnitine group (P=0.21). Of these events, 30% of those in the placebo group and 63% in the L-carnitine group were considered unrelated to the treatment. Severe adverse events occurred in 10.9% of the patients in the placebo group and 15.2% in the L-carnitine group (P=0.7). Eleven patients died during the study: four in the placebo group and seven in the L-carnitine group (P=0.3). The incidence of each adverse event did not differ significantly between the groups.

Multivariate Analysis

EPO-RI was associated with albuminemia, iron status, and nutrition supplementation (Table 2). After adjustment for these variables, EPO-RI was not associated with L-carnitine treatment. During the study period, serum albumin levels increased from 34.0±6.4 to 36.8±5.2 g/L (P=0.0045), and ferritin from 195±174 ng/ml at month 0 to 399±298 ng/ml at month 12 (P=0.0001); the increases were similar in both groups. Both factors contributed to the overall improvement of EPO-RI during the study period. Of note, oral nutritional supplementation remained associated with a higher EPO-RI, as a marker of malnutrition (Table 2).

Hypotensive episodes were associated with C-reactive protein and corrected serum calcium. After adjustment, L-carnitine treatment was not associated with any improvement in these episodes.

Discussion

The early, prophylactic use of intravenous L-carnitine for the first year of hemodialysis did not modify rHuEPO requirements. Despite carnitine supplementation, nutrition status remained a potent determinant of rHuEPO response in this population.

Some previous randomized studies suggested that carnitine would reduce the necessary EPO dose (17–20). Two main factors probably explain the difference between those studies and ours. First, we included a low percentage of patients resistant to rHuEPO, unlike previous studies, which had selected patients according to this criterion. Second, half of our placebo group consistently

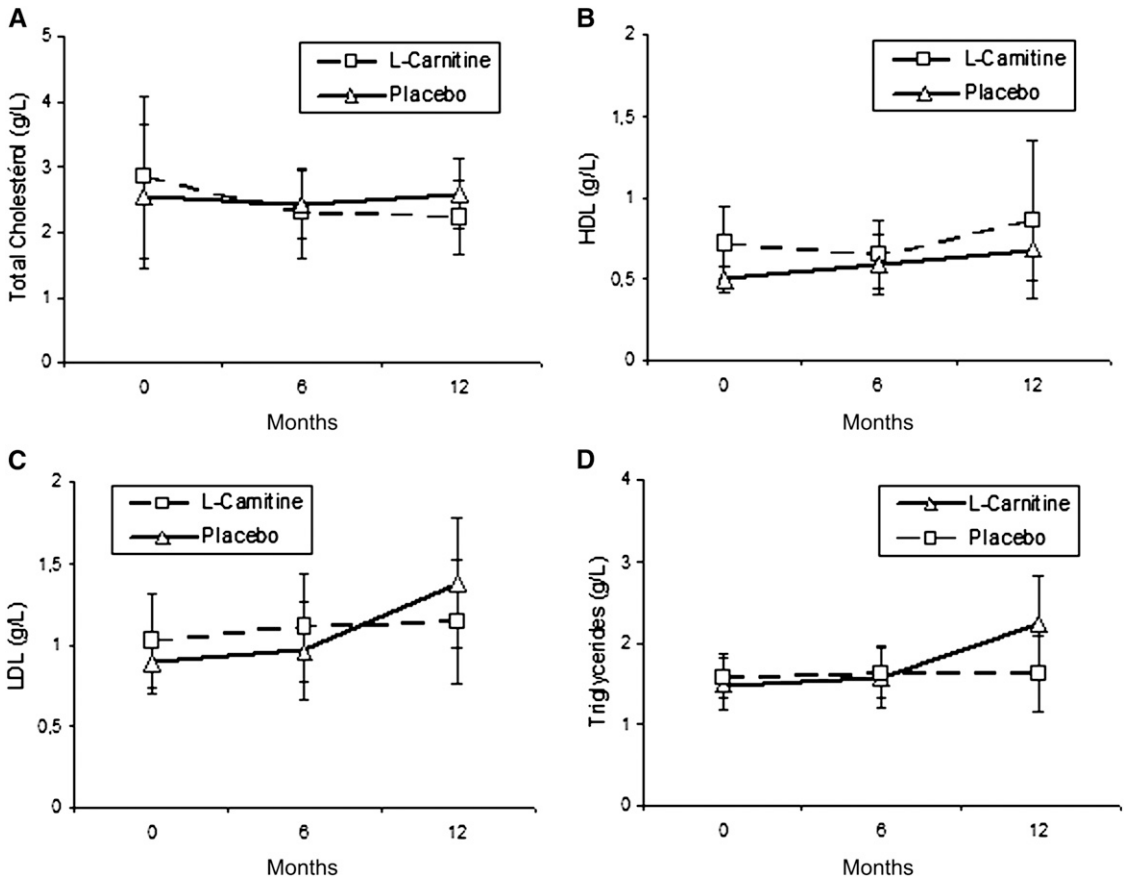

Figure 4. | **Lipid profiles in placebo and L-carnitine groups.** Error bars represent 95% confidence intervals. (A) Total cholesterol. (B) HDL cholesterol. (C) LDL cholesterol. (D) Triglycerides.

Table 2. Mixed linear model of the erythropoietin resistance index

Effect	Variations in Box-Cox EPO-RI	Standard Error	P value
L-carnitine	0.77	0.47	0.10
Time (mo)	−0.058	0.057	0.30
L-carnitine × time (mo)	0.001	0.081	0.98
Baseline rHuEPO doses (IU)	0.0002	0.00003	<0.001
Baseline hemoglobin level (g/dl)	−0.72	0.16	<0.001
Serum albumin (g/L)	−0.098	0.017	<0.001
Transferrin saturation (%)	−0.037	0.0079	<0.001
Nutritional supplement	1.35	0.43	0.001

EPO-RI, erythropoietin resistance index calculated as mean weekly recombinant human EPO doses (IU) per kg body weight divided by hemoglobin (g/dl); rHuEPO, recombinant human erythropoietin. EPO-RI was normalized by Box-Cox transformation: $(y^{0.6}-1)/-0.6$. A total of 1144 observations in 88 patients. Imputation last observation carried forward for missing values.

maintained a normal carnitine level, defined by a free carnitine level ≥30 μmol/L. Previous studies had included long-term hemodialysis patients with profound carnitine deficiencies. A current clinical trial includes hemodialysis patients with free carnitine level <40 μmol/L (25) and may determine whether L-carnitine has any effect in selected patients with carnitine deficiency.

Carnitine supplementation took place at the generally recommended dose of 1 g after each dialysis session. At this dose, we observed a rapid increase in carnitine levels, reaching levels twice as high as the physiologic concentration. No adverse effect was shown. Some reports suggest that so high a level of carnitine might influence erythropoiesis and stimulate erythroblasts (11,12), but we observed no such effect. EPO response did not differ for patients with high carnitine levels compared with those with physiologic levels.

Our study confirms the rapid decline—11%±33%—of carnitine levels in our placebo group during a 1-year period of hemodialysis, including most of the first year. In contrast, we did not observe the previously reported inversion of the ratio of free to total carnitine. The free form continued to account for 75% of total carnitine, with the remainder in acyl form. Consequently, the acyl form of carnitine also increased to a supraphysiologic level in the supplemented group. These esters are formed with acyl groups from long-chain and very-long-chain fatty acids and are needed to transport them through mitochondrial membranes. Acylcarnitine accumulation could be related to impaired mitochondrial transport or to increased formation. Recent studies have analyzed the different forms of acylcarnitine and found an association between poor outcome, inflammation, and longer acylcarnitine chains (25,26). This association was found in hemodialysis patients without L-carnitine supplementation and might reflect impaired mitochondrial transport. We cannot totally rule out such an association in our supplemented patients, although the high level in this group probably reflects forced synthesis by L-carnitine supply. The acylcarnitine profile of these patients and its relation with outcome must be examined in greater detail.

Nutrition influences anemia correction in hemodialysis by several pathways, including folic acid, vitamin B, vitamin C, carnitine, and iron deficiencies but also by a decrease in antioxidative capacity that produces a proinflammatory effect (27). In our incident hemodialysis population, some patients met some criteria for malnutrition while maintaining a persistent normal or only slightly decreased carnitine level. The carnitine pool located in the muscle may initially be protected by the nutrition improvement that we observed during the first year of hemodialysis. For malnourished patients with a more profound carnitine deficiency, carnitine supplementation may improve EPO response and so modify the latter's relation to malnutrition.

The main limitation of our study is related to the study population. Our results can be generalized only to unselected hemodialysis patients new to hemodialysis. They cannot be extended to long-term dialysis patients with more profound carnitine deficiency (2,28). These carnitine-deficient patients have a higher risk for hyporesponsive rHuEPO-dependent anemia (28). Further studies must clarify whether these patients require carnitine supplementation. The second limitation is related to the broad confidence interval for EPO-RI, which might limit our power to demonstrate a difference between groups. However, the similarity of the variance of EPO-RI in the two groups limits the likelihood of a false-negative result.

Our conclusions confirm that plasma carnitine levels decline by 11%±33% during the first year of hemodialysis. Carnitine deficiency is present in about 30% of the patients during this period with an onset as early as 3 months after initiation of hemodialysis. Malnutrition markedly influences rHuEPO response in hemodialysis patients. There is nonetheless no evidence that L-carnitine offers benefits to patients new to hemodialysis.

Acknowledgments

The authors wish to thank Sigma-Tau for supplying both L-carnitine and placebo at no cost; Karima Mesbahi, Hervé Oya, and Florence Combel for the careful data collection and management; and Jo Ann Cahn for English corrections.

This study was supported by a grant from the French Ministry of Health: CIRC 2005, P050316.

Disclosures

L.M. received honoraria from Gambro and Hoffmann-La-Roche in 2010.

References

1. Fornasini G, Upton RN, Evans AM: A pharmacokinetic model for L-carnitine in patients receiving haemodialysis. *Br J Clin Pharmacol* 64: 335–345, 2007
2. Vernez L, Dickenmann M, Steiger J, Wenk M, Krähenbühl S: Effect of L-carnitine on the kinetics of carnitine, acylcarnitines and butyrobetaine in long-term haemodialysis. *Nephrol Dial Transplant* 21: 450–458, 2006
3. Bartel LL, Hussey JL, Shrago E: Perturbation of serum carnitine levels in human adults by chronic renal disease and dialysis therapy. *Am J Clin Nutr* 34: 1314–1320, 1981
4. Sakurauchi Y, Matsumoto Y, Shinzato T, Takai I, Nakamura Y, Sato M, Nakai S, Miwa M, Morita H, Miwa T, Amano I, Maeda K: Effects of L-carnitine supplementation on muscular symptoms in hemodialyzed patients. *Am J Kidney Dis* 32: 258–264, 1998
5. Aguilar-Kitsu A, Ibarra-Cazares P, Mendoza-Guevara L, Villasis-Keever MA, Perez Andrade ME, Castillo-Romero L, Morales-Nava A, Rodriguez-Leyva F, Sanchez-Barbosa L: Frequency of low carnitine levels in children on dialysis. *Adv Perit Dial* 22: 208–210, 2006
6. Debska-Slizień A, Kawecka A, Wojnarowski K, Zadrony D, Kunicka D, Król E, Lysiak-Szydłowska W, Rutkowski B: Carnitine content in different muscles of patients receiving maintenance hemodialysis. *J Ren Nutr* 17: 275–281, 2007
7. Evans AM, Faull RJ, Nation RL, Prasad S, Elias T, Reuter SE, Fornasini G: Impact of hemodialysis on endogenous plasma and muscle carnitine levels in patients with end-stage renal disease. *Kidney Int* 66: 1527–1534, 2004
8. Duranay M, Akay H, Yilmaz FM, Şeneş M, Tekeli N, Yücel D: Effects of L-carnitine infusions on inflammatory and nutritional markers in haemodialysis patients. *Nephrol Dial Transplant* 21: 3211–3214, 2006
9. Savica V, Santoro D, Mazzaglia G, Ciolino F, Monardo P, Calvani M, Bellinghieri G, Kopple JD: L-carnitine infusions may suppress serum C-reactive protein and improve nutritional status in maintenance hemodialysis patients. *J Ren Nutr* 15: 225–230, 2005
10. Calò LA, Pagnin E, Davis PA, Semplicini A, Nicolai R, Calvani M, Pessina AC: Antioxidant effect of L-carnitine and its short chain esters: Relevance for the protection from oxidative stress related cardiovascular damage. *Int J Cardiol* 107: 54–60, 2006
11. Matsumura M, Hatakeyama S, Koni I, Mabuchi H: Effect of L-carnitine and palmitoyl-L-carnitine on erythroid colony formation in fetal mouse liver cell culture. *Am J Nephrol* 18: 355–358, 1998
12. Kitamura Y, Satoh K, Satoh T, Takita M, Matsuura A: Effect of L-carnitine on erythroid colony formation in mouse bone marrow cells. *Nephrol Dial Transplant* 20: 981–984, 2005
13. Signorelli SS, Fatuzzo P, Rapisarda F, Neri S, Ferrante M, Oliveri Conti G, Fallico R, Di Pino L, Pennisi G, Celotta G, Massimiliano A: A randomised, controlled clinical trial evaluating changes in therapeutic efficacy and oxidative parameters after treatment with propionyl L-carnitine in patients with peripheral arterial disease requiring haemodialysis. *Drugs Aging* 23: 263–270, 2006
14. Arduini A, Bonomini M, Clutterbuck EJ, Laffan MA, Pusey CD: Effect of L-carnitine administration on erythrocyte survival in haemodialysis patients. *Nephrol Dial Transplant* 21: 2671–2672, 2006
15. Kooistra MP, Struyvenberg A, van Es A: The response to recombinant human erythropoietin in patients with the anemia of end-stage renal disease is correlated with serum carnitine levels. *Nephron* 57: 127–128, 1991
16. Matsumura M, Hatakeyama S, Koni I, Mabuchi H, Muramoto H: Correlation between serum carnitine levels and erythrocyte osmotic fragility in hemodialysis patients. *Nephron* 72: 574–578, 1996
17. Labonia WD: L-carnitine effects on anemia in hemodialyzed patients treated with erythropoietin. *Am J Kidney Dis* 26: 757–764, 1995
18. Caruso U, Leone L, Cravotto E, Nava D: Effects of L-carnitine on anemia in aged hemodialysis patients treated with recombinant human erythropoietin: a pilot study. *Dial Transplant* 27: 499–506, 1998
19. Kletzmayr J, Mayer G, Legenstein E, Heinz-Peer G, Leitha T, Hörl WH, Kovarik J: Anemia and carnitine supplementation in hemodialyzed patients. *Kidney Int Suppl* 69: S93–S106, 1999
20. Steiber AL, Davis AT, Spry L, Strong J, Buss ML, Ratkiewicz MM, Weatherspoon LJ: Carnitine treatment improved quality-of-life measure in a sample of Midwestern hemodialysis patients. *JPEN J Parenter Enteral Nutr* 30: 10–15, 2006
21. Hurot JM, Cucherat M, Haugh M, Fouque D: Effects of L-carnitine supplementation in maintenance hemodialysis patients: A systematic review. *J Am Soc Nephrol* 13: 708–714, 2002
22. Vernez L, Wenk M, Krähenbühl S: Determination of carnitine and acylcarnitines in plasma by high-performance liquid chromatography/electrospray ionization ion trap tandem mass spectrometry. *Rapid Commun Mass Spectrom* 18: 1233–1238, 2004
23. Eknoyan G, Latos DL, Lindberg J; National Kidney Foundation Carnitine Consensus Conference: Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder. *Am J Kidney Dis* 41: 868–876, 2003
24. KDOQI Clinical Practice guidelines for nutrition in children with CKD: 2008 update. Recommendation 9: carnitine. *Am J Kidney Dis* 53[3 suppl 2]: S75–S76, 2009
25. Murphy WJA, Steiber A, Connery GC, Carder J, Spry L, Hoppel C: Altered carnitine metabolism in dialysis patients with reduced physical function may be due to dysfunctional fatty acid oxidation. *Nephrol Dial Transplant* 27: 304–310, 2012
26. Adams SH, Hoppel CL, Lok KH, Zhao L, Wong SW, Minkler PE, Hwang DH, Newman JW, Garvey WT: Plasma acylcarnitine profiles suggest incomplete long-chain fatty acid β-oxidation and altered tricarboxylic acid cycle activity in type 2 diabetic African-American women. *J Nutr* 139: 1073–1081, 2009
27. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD: Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am J Clin Nutr* 80: 299–307, 2004
28. Reuter SE, Faull RJ, Ranieri E, Evans AM: Endogenous plasma carnitine pool composition and response to erythropoietin treatment in chronic haemodialysis patients. *Nephrol Dial Transplant* 24: 990–996, 2009

Received: December 7, 2011 **Accepted:** June 22, 2012

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "L-Carnitine for Anemia in Hemodialysis Patients: A Last Resort," on pages 1746–1748.