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Carnitine Therapy Is Associated with Decreased Hospital Utilization among Hemodialysis Patients

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Key Words
Carnitine · Dialysis · End-stage kidney disease · Hospitalization · Carnitine therapy

Abstract
Background/Aims: Hospitalizations account for 41% of the total cost of end-stage renal disease (ESRD) care. Carnitine deficiency is common among dialysis patients, and some studies have shown improvements in anemia, and cardiac and skeletal muscle function upon administration of *L*-carnitine. We hypothesized that *L*-carnitine may be associated with decreased hospital utilization in these patients. ***Methods:*** The Fresenius Medical Care North America dialysis database was used for this retrospective analysis. Adult patients who received carnitine for at least 3 months, and had at least 3 months of pre-carnitine follow-up were included in the study. Hospitalization and hospital day rates were compared before and during carnitine therapy, and with a matched population. ***Results:*** Carnitine therapy at a mean dose of 1.5 ± 0.7 g per administration for an average of 9.7 ± 5.4 months was associated with a significant reduction in hospital utilization. Patients with cardiovascular disease, defined as hospitalizations for angina, myocardial infarction, arrhythmia, congestive heart failure, cerebral vascular disease or peripheral vascular disease prior to receiving carnitine, and those with anemia and hypoalbuminemia derived the greatest benefit from carnitine therapy. In a multivariate analysis, compared to 3 months prior to the initiation of carnitine, the adjusted relative risk for hospitalization was 11, 11, and 15% lower at 3, 6, and 9 months, respectively. Among patients with cardiovascular disease, the reduction in risk was even more significant (24, 31, and 34% lower at 3, 6, and 9 months, respectively). Similar results were observed with adjusted relative risk for hospital days. ***Conclusion:*** Administration of *L*-carnitine to chronic hemodialysis patients is associated with lower hospital utilization.

Introduction

Patients with end-stage renal disease (ESRD) experience high morbidity and consume a significant proportion of healthcare resources. Between 1996 and 1998, the

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average ESRD patient had 1.9 hospitalizations and spent 14 days in hospital per year [1]. In contrast, individuals in the general population only had 0.31 hospitalizations and spent 1.9 days in hospital in 1998 [2]. The total annual cost of care of the ESRD population in the USA was estimated to be USD 17.9 billion in 1999 [3]. Hospitalizations account for 41% of the ESRD cost, and hence, are a prime target for reduction in resource utilization and cost containment [4]. In an earlier study of dialysis patients, cardiovascular disease was the second largest cause of hospitalization and accounted for the highest number of days spent in the hospital [5].

Carnitine deficiency is common among chronic hemodialysis patients and is due to increased losses during the dialysis procedure and possibly low dietary intake and endogenous production [6, 7]. The main cellular function of *L*-carnitine is to facilitate the entry of long-chain fatty acids into the mitochondria for oxidation, and to provide energy in the form of ATP [8, 9]. Since cardiac and skeletal muscle metabolism is largely oxidative and dependent on free fatty acid delivery and mitochondrial transport, and since myocytes have one of the highest carnitine concentrations of the body, correction of carnitine deficiency could result in improved cardiac function [10, 11]. Indeed, experimental models of cardiomyopathy have been corrected with the administration of *L*-carnitine, primary carnitine deficiency has been associated with the development of left ventricular hypertrophy in animal models, and some clinical studies have shown improvement in survival and/or cardiac function upon administration of *L*-carnitine to patients with heart failure or acute myocardial infarction [12–14]. In addition, several abnormalities of fatty acid metabolism, such as high concentrations of plasma free fatty acids due to enhanced degradation of triglycerides, correlate with cardiac arrhythmias and appear to be reversible by carnitine therapy in dialysis patients [15].

Higher serum carnitine levels have also been associated with higher hematocrit levels in non-rHuEPO-treated patients, and with reduced rHuEPO requirements in patients on maintenance rHuEPO therapy [16]. Anemia is an independent risk factor for the development of heart failure and a predictor of mortality in hemodialysis patients [17]. rHuEPO resistance has been associated with congestive heart failure and dialysis-related hypotension [18]. In view of the potential improvements in cardiac function and anemia, we hypothesized that carnitine therapy could result in reduced hospitalization rates among chronic hemodialysis patients.

In the present study we used a large cohort of chronic hemodialysis patients and found that administration of *L*-carnitine was associated with reduced hospital utilization.

Subjects and Methods

Patient Population

This is a retrospective analysis of data obtained from Fresenius Medical Care (FMC) North America, a US national provider of dialysis services. The subjects included in this study were all adult patients aged 18 years or older, who had started dialysis after October 30, 1996. Additional inclusion criteria included all of the following: at least 3 months of pre-carnitine follow-up, at least one required laboratory measurement in the 3 months prior to the first carnitine administration, and carnitine therapy for at least 3 consecutive months. Kidney transplant recipients were excluded from the analysis. The Institutional Review Board of Tufts-New England Medical Center approved the study.

Data Sources

Data were obtained from the electronic databases of FMC. *The Patient File* contained demographic information, the dates of the first and last carnitine administration, and clinical information such as diabetic status and reason for carnitine administration. *The Admission File* contained dates of admission and discharge from FMC, including the reason for discharge from the clinic (e.g., died, transplant, recovered, transferred, lost to follow-up). *The Temporary Absence File* contained the start and end dates of all temporary absences including morbidity-related events occurring after October 30, 1996. If a hospitalization occurred, the data file also contained the ICD-9 code for the primary reason for hospitalization. *The Lab Results File* contains laboratory information for each patient, such as albumin and hemoglobin. *The Carnitine Dosage File* has information on total monthly carnitine dose and the total number of monthly carnitine administrations.

Definitions and Data Categorization

Patient age was categorized as 18–44, 45–64, 65–74, or ≥75 years. Race was categorized as Caucasian, African-American, or other. Cause of ESRD was classified as diabetes mellitus, hypertension, glomerular, and other. Comorbid conditions considered were diabetes mellitus and cardiovascular disease. The latter was defined as any hospitalization recorded in the *Temporary Absence* file with a diagnosis of angina, myocardial infarction, arrhythmia, congestive heart failure, cerebral vascular disease or peripheral vascular disease prior to receiving carnitine. Anemia was defined as a hemoglobin level <11 g/dl. Hypoalbuminemia was defined as a serum albumin level <3.5 g/dl. Reasons for initiation of carnitine therapy were categorized as cardiac, muscular, anemia, or other. The most frequent reasons were muscular wasting and disuse (37.8%), secondary cardiomyopathy (21.7%), anorexia (5%), and anemia (3%). Other reasons included dialysis hypotension, malnutrition, fatigue and malaise, and other less specific causes. Duration of carnitine was calculated as the number of months between the first and last dose of carnitine, which was then categorized as 3–6, 6–12, and >12 months. The average dose of carnitine for each patient was esti-

mated by dividing the total dose of carnitine by the total number of carnitine administrations.

Statistical Analysis

Summary descriptive statistics of the relevant patient characteristics were performed for the study sample. Results of continuous variables are presented as mean ± SD. For discrete variables the results are presented as percentages. Correlations were calculated using the Spearman correlation coefficient.

In order to determine whether carnitine had an effect on the rates of hospitalization and hospital days, a 'total time at risk period' was defined for each patient and the number of hospitalizations and total duration of hospital stay were calculated over successive 3-month periods. The 'total time at risk period' was defined as at least 3 months and up to 1 year prior to the first carnitine dose to the last carnitine dose, death, loss to follow-up, or end of the study period (December 31, 2000). All patients did not have a complete 12-month of pre-carnitine data. For these patients, time at risk was calculated starting either from the first date of chronic dialysis at FMC or October 31, 1996, whichever came last. Next, the 'total time at risk' was divided into successive 3-month intervals using the first carnitine administration date as the start date. Unadjusted hospitalization rates over successive 3-month periods were calculated by summing up the total number of hospitalizations within each 3-month interval, and dividing by the total number of person-months during the interval. The total number of days absent from FMC due to hospitalizations was subtracted from the time at risk for hospital days. Unadjusted risk ratios of hospitalization in successive 3-month intervals, before and after initiation of carnitine therapy were reported using the hospitalization rate 3 months prior to initiation of carnitine as the reference group. The same approach was used for the outcome of total hospital days. We elected to examine both hospitalizations and hospital days because they provide a more complete picture of hospital utilization. Since few patients received carnitine for longer than 24 months, results are only reported up to a maximum of 2 years from the first carnitine administration.

In addition to the strategy of using the same patients as their own controls to compare hospitalization and hospital day rates before and during carnitine therapy, a control group was designed specifically to address the concerns of 'regression to the mean phenomenon' and 'survival bias'. A population of patients admitted to FMC clinics who had never received carnitine were matched to the 2,967 cases (a cohort of patients who neither died nor was lost to follow-up 6 months pre- and during carnitine therapy). Control subjects were pair-matched to the cases by age (within 10 years), gender, race, diabetes status, the year dialysis was started, total duration of dialysis (within 1 year), and hospitalization rate over the entire time at risk (within at least 1 hospitalization per year). The 'total time at risk period' for controls was defined as the start of dialysis to discharge from FMC or end of the study period (December 12, 2000). The overall hospitalization rate for both cases and controls was calculated using the total number of hospitalizations for a patient divided by the total person time minus time hospitalized. All controls were required to have at least 12 months of follow-up at the FMC clinic.

To examine risk factors for hospitalizations and number of hospital days, a generalized estimating equation (GEE) analysis was performed. The outcome was either the total number of hospitalizations or the total number of hospital days within the 3-month interval. Independent variables tested in the univariate and multivariate models included age, gender, race, cause of ESRD, carnitine duration, carnitine dose, reason for carnitine use, time on dialysis before initiation of carnitine, comorbidities (diabetes, cardiovascular), hemoglobin, and serum albumin. The predictors of interest were the risk of hospitalization and hospital days in each 3-month interval in the pre-carnitine and carnitine periods, using the –3 to 0 months risk as the reference group. The GEE model was performed in two populations, the overall cohort and that of patients with cardiovascular disease. Goodness of fit was inspected by comparing predicted and observed rate ratios. Data management and statistical analyses were performed using the SAS system for Windows Version 8.2.

Table 1. Characteristics of hemodialysis patients who received carnitine therapy between October 31, 1996 and December 31, 2000

Mean age, years	65.1 ± 14.1
Male, %	52
Race, %	
Caucasian	57
African-American	34
Other	9
Cause of ESRD, %	
Diabetes mellitus	37
Hypertension	40
Glomerular disease	8
Other	15
Comorbid conditions, %	
Diabetes mellitus	59
Cardiovascular disease	35
Laboratory values, g/dl	
Mean hemoglobin	11.3 ± 1.3
Mean serum albumin	3.7 ± 0.4
Mean time on dialysis, years	1.7 ± 1.1
Mean dose of carnitine, g	1.5 ± 0.7
Mean duration of carnitine therapy, months	9.7 ± 5.4
Reasons for initiation of carnitine therapy, %	
Musculoskeletal problems	43
Cardiovascular disease	25
Other causes	29
Anemia	3

Results

A total of 2,990 adult (≥ 18 years) patients fulfilled the inclusion criteria. Twenty-three patients were excluded because they received a kidney transplant or had a total hospitalization time in a given 3-month period exceeding 90 days. Thus, the final study population consisted of 2,967 patients.

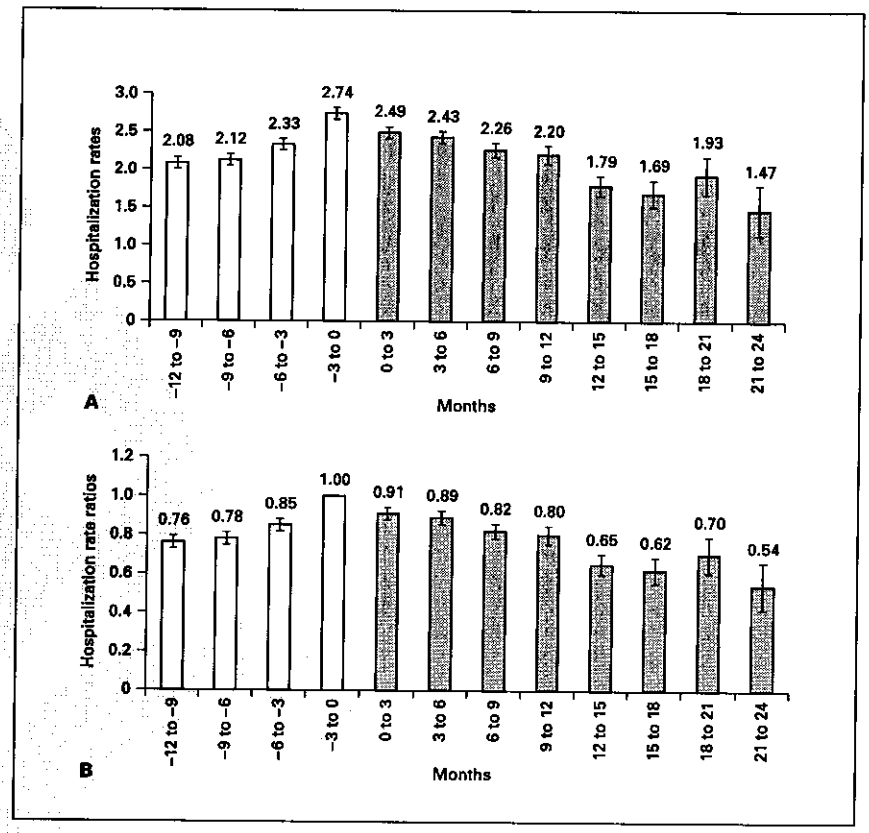

Fig. 1. Unadjusted rates (**A**) and rate ratios (**B**) of hospitalization per patient-year at risk before and during treatment with *L*-carnitine. □ = Before carnitine, ▨ = during carnitine.

Patient Characteristics

The mean age of the patients was 65.1 ± 14.1 years, 48% were female, and 57% were Caucasians. Fifty-nine percent had diabetes and 35% had cardiovascular disease. The cause of ESRD was hypertension in 40%, diabetes in 37%, glomerular disease in 8%, and other causes in 15%. The mean follow-up during the pre-carnitine period was 10.5 ± 2.6 months (max. 12 months, min. 3 months). The average duration of carnitine use was 9.7 ± 5.4 months, which was also the average follow-up period during carnitine treatment. The mean duration on dialysis before the initiation of carnitine was 1.7 ± 1.1 years. The mean dose of carnitine was 1.5 ± 0.7 g per administration. The reasons for carnitine administration were muscular in 43%, cardiac in 25%, anemia in 3%, and other reasons in 29% of patients (table 1). A total of 571 patients (19.2%) died during the course of the study.

Hospitalization

Overall, patients had an average of 2.3 hospitalizations per patient-year at risk. During the pre-carnitine period, the unadjusted rates of hospitalization per patient-year at risk increased from 2.08 at –12 to –9 months to 2.74 at –3 to 0 months. During the carnitine period, the unadjusted rates of hospitalization per patient-year at risk decreased to 2.49 at 0–3 months and to 2.43 at 3–6 months, and continued to decrease thereafter (fig. 1A). Compared to the hospitalization rate at –3 to 0 months in the pre-carnitine period, the hospitalization rate ratios during the carnitine period decreased to 0.91 at 0–3 months, 0.89 at 3–6 months and to 0.80 at 9–12 months (fig. 1B). Patients younger than 65 years of age and those with cardiovascular disease, anemia, or hypoalbuminemia had lower hospitalization rates in the carnitine period compared to the pre-carnitine period (table 2).

Hospital Days

There was a strong correlation between number of hospitalizations and number of hospital days (Spearman correlation 0.89, $p < 0.0001$). Overall, patients spent 16 days in the hospital per patient-year at risk. During the pre-carnitine period, the unadjusted rates of hospital days per

Table 2. Mean number of hospitalizations per patient-year at risk before and during carnitine use

	Pre-carnitine	During carnitine	Rate ratio	95% CI
Overall	2.41	2.32	0.96	0.90, 1.02
Age, years				
18–44	2.84	2.29	0.81	0.69, 0.95
45–64	2.53	2.24	0.89	0.82, 0.96
65–74	2.26	2.48	1.09	1.00, 1.20
75+	2.05	2.15	1.05	0.95, 1.16
Gender				
Female	2.47	2.40	0.97	0.92, 1.05
Male	2.23	2.19	0.98	0.90, 1.04
Race				
Caucasian	2.35	2.31	0.98	0.92, 1.04
African-American	2.35	2.33	0.99	0.90, 1.07
Other	2.26	2.03	0.90	0.75, 1.07
Cause of ESRD				
Diabetes mellitus	2.42	2.39	0.99	0.92, 1.04
Hypertension	2.34	2.26	0.97	0.89, 1.04
Glomerular disease	2.49	2.26	0.91	0.76, 1.10
Other	2.12	2.18	1.03	0.90, 1.16
Diabetes mellitus				
Yes	2.47	2.45	0.99	0.93, 1.06
No	2.16	2.08	0.96	0.88, 1.04
Cardiovascular disease				
Yes	3.56	2.97	0.83	0.77, 0.89
No	1.65	1.95	1.18	1.10, 1.26
Hemoglobin, g/dl				
≤11	3.01	2.81	0.93	0.87, 1.00
>11	1.95	1.98	1.01	0.94, 1.09
Serum albumin, g/dl				
<3.5	3.49	3.10	0.89	0.81, 0.96
≥3.5	1.99	2.05	1.03	0.97, 1.09
Time on dialysis before carnitine, years				
<1	3.09	2.68	0.87	0.74, 1.02
1–2	2.43	2.26	0.93	0.85, 1.01
2–3	2.30	2.32	1.01	0.92, 1.10
3–4	2.15	2.22	1.04	0.92, 1.16
4	1.98	1.54	0.78	0.61, 1.00
Duration of carnitine therapy, months				
3–6	2.47	2.63	1.06	0.96, 1.18
6–12	2.33	2.42	1.04	0.96, 1.12
>12	2.22	2.11	0.95	0.88, 1.07
Reasons for initiation of carnitine therapy				
Musculoskeletal problems	2.24	2.24	1.00	0.92, 1.07
Cardiovascular disease	2.39	2.22	0.93	0.84, 1.02
Other causes	2.39	2.32	0.97	0.88, 1.06
Anemia	3.04	3.58	1.18	0.90, 1.51

Table 3. Mean number of hospital days per patient-year at risk before and during carnitine use

	Pre-carnitine	During carnitine	Rate ratio	95% CI
Overall	17.0	15.7	0.92	0.85, 1.00
Age, years				
18–44	18.8	14.6	0.78	0.63, 0.95
45–64	17.0	15.1	0.89	0.79, 1.00
65–74	16.4	17.6	1.07	0.95, 1.20
75+	14.5	14.4	0.99	0.87, 1.12
Gender				
Female	18.1	16.8	0.93	0.85, 1.02
Male	14.7	14.5	0.99	0.90, 1.09
Race				
Caucasian	16.5	15.7	0.95	0.88, 1.04
African-American	16.0	16.1	1.01	0.89, 1.12
Other	16.5	13.0	0.79	0.62, 1.01
Cause of ESRD				
Diabetes mellitus	18.0	17.9	1.00	0.90, 1.11
Hypertension	15.1	13.9	0.92	0.83, 1.02
Glomerular disease	17.8	14.3	0.81	0.64, 1.02
Other	14.5	15.1	1.04	0.87, 1.23
Diabetes mellitus				
Yes	17.7	17.8	1.01	0.92, 1.10
No	14.5	12.6	0.87	0.78, 0.98
Cardiovascular disease				
Yes	25.2	20.6	0.82	0.75, 0.90
No	11.2	13.0	1.16	1.05, 1.28
Hemoglobin, g/dl				
≤11	21.6	19.4	0.90	0.82, 1.00
>11	13.2	13.3	1.00	0.92, 1.10
Serum albumin, g/dl				
<3.5	27.9	21.9	0.79	0.70, 0.88
≥3.5	12.8	13.7	1.07	0.99, 1.16
Time on dialysis before carnitine, years				
<1	21.8	16.9	0.77	0.63, 0.96
1–2	17.4	15.9	0.91	0.81, 1.02
2–3	15.4	16.2	1.05	0.94, 1.18
3–4	14.7	14.6	0.99	0.85, 1.15
4	14.8	9.4	0.63	0.46, 0.87
Dose of carnitine				
(per 1 g increase)	17.0	15.7	0.92	0.85, 1.00
Duration of carnitine therapy, months				
3–6	17.8	18.5	1.03	0.90, 1.18
6–12	16.6	16.7	1.01	0.90, 1.12
>12	14.3	13.9	0.98	0.88, 1.10
Reasons for initiation of carnitine therapy				
Musculoskeletal problems	15.5	14.9	0.96	0.87, 1.06
Cardiovascular disease	17.7	16.3	0.92	0.81, 1.05
Other causes	16.1	15.6	0.97	0.85, 1.10
Anemia	18.1	19.0	1.05	0.75, 1.49

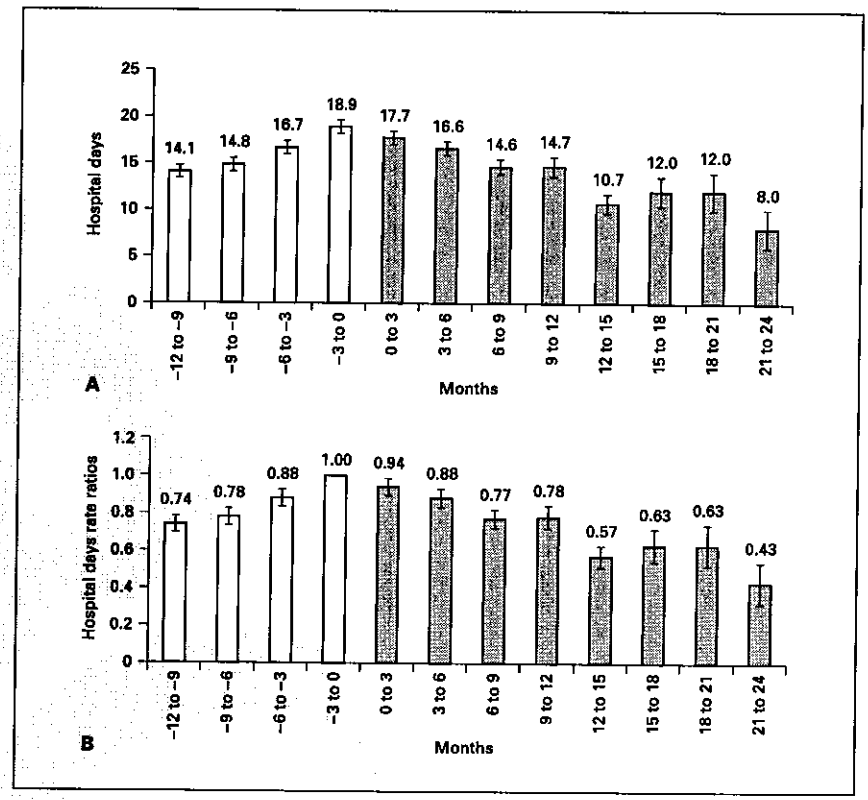

Fig. 2. Unadjusted rates (**A**) and rate ratios (**B**) of hospital days per patient-year at risk before and during treatment with *L*-carnitine. □ = Before carnitine, ▨ = during carnitine.

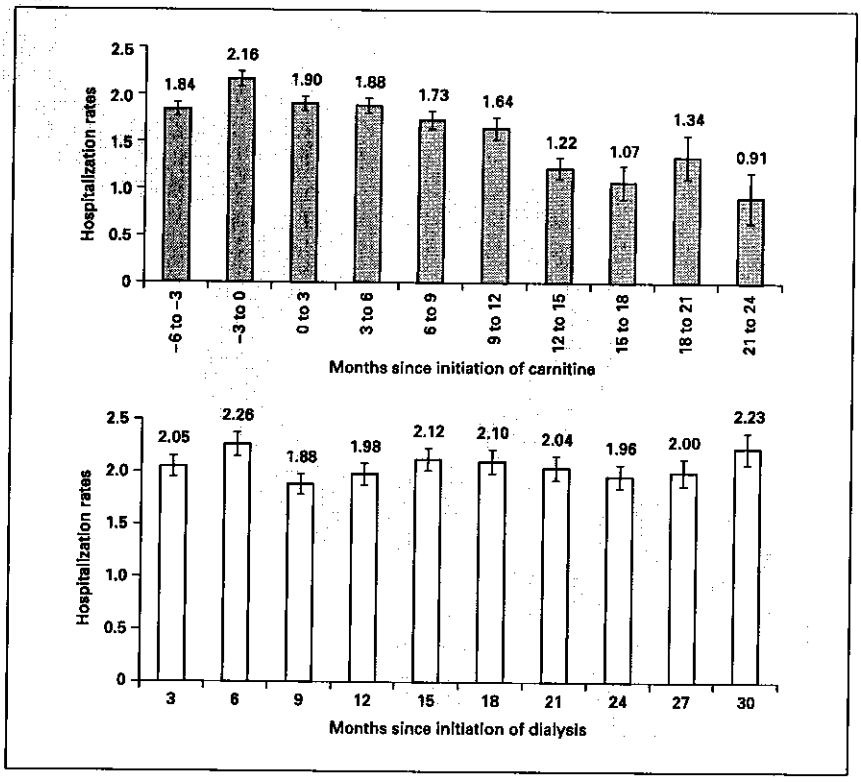

Fig. 3. Unadjusted rates of hospitalization per patient-year at risk in cases (▨) and matched controls (□).

Table 4. Multivariate analysis of risk factors for hospitalization in the overall cohort and in the subset of patients with cardiovascular disease

	Overall cohort		Cardiac cohort	
	relative risk	95% CI	relative risk	95% CI
Age, years				
18–44	1.20	1.05, 1.36	1.35	1.13, 1.61
45–64	1.10	1.00, 1.20	1.17	1.04, 1.32
65–74	1.09	1.00, 1.20	1.15	1.02, 1.30
75+	1.00	–	1.00	–
Gender				
Female	1.02	0.96, 1.09	1.02	0.92, 1.11
Male	1.00	–	1.00	–
Race				
Caucasian	0.96	0.89, 1.04	0.97	0.97, 1.07
African-American	0.97	0.86, 1.10	0.96	0.80, 1.15
Other	1.00	–	1.00	–
Cause of ESRD				
Diabetes mellitus	1.10	0.98, 1.23	1.13	0.97, 1.32
Hypertension	1.11	1.00, 1.23	1.15	1.00, 1.32
Glomerular disease	1.16	0.99, 1.37	1.18	0.97, 1.46
Other	1.00	–	1.00	–
Diabetes mellitus				
Yes	1.12	1.03, 1.22	1.11	0.99, 1.25
No	1.00	–	1.00	–
Cardiovascular disease				
Yes	1.91	1.79, 2.50	–	–
No	1.00	–	–	–
Hemoglobin, g/dl				
≤11	1.31	1.23, 1.40	1.28	1.17, 1.41
>11	1.00	–	1.00	–
Serum albumin, g/dl				
<3.5	1.41	1.32, 1.50	1.28	1.16, 1.41
≥3.5	1.00	–	1.00	–
Time on dialysis before carnitine, years				
<1	1.63	1.38, 1.93	2.01	1.58, 2.56
1–2	1.38	1.20, 1.60	1.62	1.33, 1.96
2–3	1.36	1.17, 1.56	1.46	1.21, 1.76
3–4	1.32	1.13, 1.53	1.27	1.04, 1.55
4	1.00	–	1.00	–
Dose of carnitine (per 1 g increase)	0.97	0.92, 1.02	0.99	0.92, 1.06
Duration of carnitine therapy, months				
3–6	1.09	1.00, 1.19	1.03	0.91, 1.16
6–12	1.04	0.96, 1.13	0.99	0.88, 1.10
>12	1.00	–	1.00	–
Reasons for initiation of carnitine therapy				
Musculoskeletal problems	1.01	0.93, 1.09	1.02	0.91, 1.13
Cardiovascular disease	0.99	0.91, 1.08	1.02	0.91, 1.15
Anemia	1.29	1.09, 1.54	1.35	1.05, 1.73
Other causes	1.00	–	1.00	–
Time (before and during carnitine), months				
−12 to −9	0.76	0.69, 0.83	0.72	0.64, 0.82
−9 to −6	0.78	0.71, 0.84	0.76	0.68, 0.86
−6 to −3	0.85	0.79, 0.92	0.81	0.73, 0.91
−3 to 0	1.00	–	1.00	–
0 to +3	0.89	0.83, 0.96	0.76	0.69, 0.85
+3 to +6	0.89	0.82, 0.97	0.69	0.62, 0.77
+6 to +9	0.85	0.77, 0.93	0.66	0.57, 0.76
+9 to +12	0.81	0.72, 0.91	0.66	0.56, 0.77
+12 to +15	0.67	0.57, 0.79	0.52	0.40, 0.67
+15 to +18	0.65	0.51, 0.81	0.42	0.30, 0.58
+18 to +21	0.72	0.55, 0.94	0.61	0.41, 0.89
+21 to +24	0.59	0.37, 0.95	0.66	0.33, 1.29

Table 5. Multivariate analysis of risk factors for hospital days in the overall cohort and in the subset of patients with cardiovascular disease

	Overall cohort		Cardiac cohort	
	relative risk	95% CI	relative risk	95% CI
Age, years				
18–44	1.10	0.93, 1.30	1.17	0.93, 1.48
45–64	1.05	0.94, 1.18	1.14	0.97, 1.34
65–74	1.14	1.02, 1.27	1.24	1.06, 1.45
75+	1.00	–	1.00	–
Gender				
Female	1.08	0.99, 1.17	1.04	0.92, 1.17
Male	1.00	–	1.00	–
Race				
Caucasian	1.00	–	1.00	–
African-American	0.99	0.90, 1.09	1.02	0.89, 1.18
Other	0.97	0.84, 1.13	0.96	0.77, 1.18
Cause of ESRD				
Diabetes mellitus	1.12	0.97, 1.30	1.22	0.99, 1.49
Hypertension	0.99	0.88, 1.13	1.11	0.93, 1.32
Glomerular disease	1.18	0.96, 1.45	1.32	1.00, 1.32
Other	1.00	–	1.00	–
Diabetes mellitus				
Yes	1.19	1.07, 1.33	1.14	0.98, 1.33
No	1.00	–	1.00	–
Cardiovascular disease				
Yes	1.94	1.78, 2.11	–	–
No	1.00	–	–	–
Hemoglobin, g/dl				
≤11	1.35	1.24, 1.47	1.36	1.20, 1.53
>11	1.00	–	1.00	–
Serum albumin, g/dl				
<3.5	1.63	1.49, 1.78	1.42	1.25, 1.61
≥3.5	1.00	–	1.00	–
Time on dialysis before carnitine, years				
<1	1.45	1.18, 1.80	1.83	1.30, 2.57
1–2	1.37	1.14, 1.65	1.57	1.21, 2.04
2–3	1.27	1.06, 1.53	1.40	1.08, 1.81
3–4	1.22	1.01, 1.48	1.16	0.89, 1.50
4	1.00	–	1.00	–
Dose of carnitine (per 1 g increase)	0.96	0.89, 1.02	0.98	0.90, 1.07
Duration of carnitine therapy, months				
3–6	1.16	1.04, 1.30	1.06	0.91, 1.23
6–12	1.08	0.97, 1.20	0.99	0.85, 1.15
>12	1.00	–	1.00	–
Reasons for initiation of carnitine therapy				
Musculoskeletal problems	1.03	0.93, 1.14	1.10	0.96, 1.27
Cardiovascular disease	1.08	0.96, 1.20	1.12	0.96, 1.30
Anemia	1.06	0.84, 1.34	1.13	0.83, 1.54
Other causes	1.00	–	1.00	–
Time (before and during carnitine), months				
−12 to −9	0.74	0.65, 0.84	0.71	0.60, 0.84
−9 to −6	0.79	0.70, 0.89	0.79	0.67, 0.93
−6 to −3	0.88	0.79, 0.98	0.84	0.72, 0.97
−3 to 0	1.00	–	1.00	–
0 to +3	0.93	0.84, 1.03	0.79	0.69, 0.91
+3 to +6	0.88	0.78, 0.99	0.67	0.57, 0.80
+6 to +9	0.82	0.72, 0.94	0.66	0.55, 0.80
+9 to +12	0.82	0.70, 0.97	0.68	0.54, 0.86
+12 to +15	0.60	0.48, 0.74	0.44	0.32, 0.60
+15 to +18	0.68	0.51, 0.90	0.40	0.27, 0.60
+18 to +21	0.71	0.49, 1.02	0.45	0.29, 0.70
+21 to +24	0.50	0.29, 0.83	0.57	0.27, 1.17

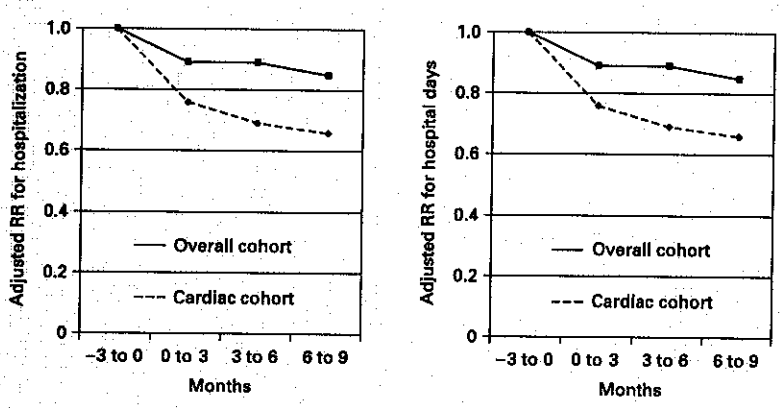

Fig. 4. Adjusted relative risk for hospitalization and hospital days in the overall cohort and in the subset of patients with cardiovascular disease.

patient-year at risk increased from 14.1 at –12 to –9 months to 18.9 at –3 to 0 months. During the carnitine period, the unadjusted rates of hospital days per patient-year at risk decreased to 17.7 at 0–3 months and to 16.6 at 3–6 months, and continued to decrease thereafter (fig. 2A). Compared to the rate of hospital days at –3 to 0 months in the pre-carnitine period, the hospital days rate ratios during the carnitine period decreased to 0.94 at 0–3 months, 0.88 at 3–6 months and to 0.78 at 9–12 months (fig. 2B). Younger patients (18–44 years), non-diabetics, those with cardiovascular disease, anemia or hypoalbuminemia, and those with <1 year or >4 years of dialysis before the initiation of carnitine, had lower number of hospital days per patient-year at risk in the carnitine period compared to the pre-carnitine period (table 3).

Matched Control Group

A total of 2,051 dialysis patients who did not receive carnitine were matched to 2,967 cases by age (within 10 years), gender, race, diabetes status, the year dialysis was started, total duration of dialysis (within 1 year), and hospitalization rate over the entire time at risk (within at least 1 hospitalization per year). As shown in figure 3, the hospitalization rates remained steady in the controls, but gradually decreased in the cases.

Risk Factors for Hospitalization

In a multivariate regression analysis, the following factors were independently associated with a higher risk for hospitalization: age 18–44 years, diabetes, cardiovascular disease, anemia (hemoglobin <11 g/dl), hypoalbuminemia (serum albumin <3.5 g/dl), shorter time on dialysis, and anemia as the reason for initiation of carnitine therapy (table 4). Compared to the hospitalization rate in the 3 months prior to the initiation of carnitine, the adjusted relative risk for hospitalization in the carnitine period at 0–3, 3–6, and 6–9 months was 0.89 (95% CI 0.83, 0.96), 0.89 (95% CI 0.82, 0.97), and 0.85 (95% CI 0.77, 0.93), respectively, and continued to decrease thereafter. When the multivariate analysis was restricted to patients with cardiovascular disease, the adjusted relative risk for hospitalization in the carnitine period at 0–3, 3–6, and 6–9 months was 0.76 (95% CI 0.62, 0.77), 0.69 (95% CI 0.62, 0.77), and 0.66 (95% CI 0.57, 0.76), respectively, and continued to decrease thereafter.

In another multivariate regression analysis, the following factors were independently associated with a higher risk for hospital days: age 65–74 years, diabetes mellitus, cardiovascular disease, anemia (hemoglobin <11 g/dl), hypoalbuminemia, shorter time on dialysis, and use of carnitine for 3 to 6 months (table 5). Compared to the hospital days rate in the 3 months prior to the initiation of carnitine, the adjusted relative risk for hospital days in the carnitine period at 0 to 3, 3 to 6, and 6 to 9 months was 0.93 (95% CI 0.84, 1.03), 0.88 (95% CI 0.78, 0.99), and 0.82 (95% CI 0.72, 0.94), respectively, and continued to decrease thereafter. When the multivariate analysis was restricted to patients with cardiovascular disease, the adjusted relative risk for hospital days in the carnitine period at 0–3, 3–6, and 6–9 months was 0.79 (95% CI 0.69, 0.91), 0.67 (95% CI 0.57, 0.80), and 0.66 (95% CI 0.55, 0.80), respectively, and continued to decrease thereafter.

Discussion

In this large cohort of hemodialysis patients, the average rate of hospitalization was 2.3 and of hospital days 16 per patient-year at risk. Carnitine therapy, which was mainly initiated for muscular (43%), cardiac (25%), and anemia (3%) reasons, was associated with a significant reduction in the rates of hospitalization and of hospital days. Patients with cardiovascular disease, anemia, and hypoalbuminemia derived the greatest benefit from carnitine therapy. In a multivariate analysis of risk factors for hospitalization, carnitine therapy was independently associated with reduced hospitalization rates. Compared to 3 months prior to the initiation of carnitine, the adjusted relative risk for hospitalization was 11, 11, and 15% lower at 3, 6, and 9 months, respectively. Among patients with cardiovascular disease, the reduction in relative risk was even more significant (24, 31, and 34% lower at 3, 6, and 9 months, respectively). In a multivariate analysis of risk factors for hospital days, carnitine therapy was independently associated with reduced hospital days. Compared to 3 months prior to the initiation of carnitine, the adjusted relative risk for hospital days was 7, 12, and 18% lower at 3, 6, and 9 months, respectively. Among patients with cardiovascular disease, the reduction in relative risk was also more significant (21, 33, and 34% lower at 3, 6, and 9 months, respectively).

The mean hospitalizations (2.3 per patient-year at risk) and hospital days (16 per patient-year at risk) found in this study were higher than those reported by the United States Renal Data System (USRDS) (1.9 and 14 days, respectively) [1]. However, this finding is not unexpected, as it was a sicker group of patients by virtue of the fact that they were given carnitine. Carnitine therapy, at a mean intravenous dose of 1.5 ± 0.7 g per administration for an average of 9.7 ± 5.4 months (the recommended dose is 20 mg/kg total body weight administered after each dialysis), was associated with lower rates of both hospitalization and hospital days. Interestingly, patients with cardiovascular disease, anemia, and hypoalbuminemia derived the greatest benefit from carnitine therapy. The presumed effects of *L*-carnitine on cardiac function and anemia could potentially explain the lower rates of hospitalization and of hospital days observed in this study.

With the exception of older age, gender, and race, the multivariate analysis identified the same risk factors for hospitalization reported elsewhere [5, 19, 20]. Although dose of carnitine was not statistically significant in any of the two models, a shorter duration of carnitine use (3–6 months) was associated with a higher risk of hospital days. A trend towards an association between shorter duration of carnitine use and higher risk for hospitalization was also observed. Lastly, after adjusting for cardiovascular disease, anemia, hypoalbuminemia, and other risk factors, carnitine therapy remained independently associated with a lower risk for hospitalization and for hospital days at successive time intervals, and the effect was even more significant in the subset of patients with cardiovascular disease.

Potential reasons for administering *L*-carnitine in maintenance hemodialysis patients include dyslipidemia, muscle weakness, cardiac symptoms, and anemia. In a recent pooled analysis of 18 clinical trials involving 482 maintenance hemodialysis patients, no effect of *L*-carnitine was observed on triglycerides, total cholesterol, or any of its fractions. However, *L*-carnitine treatment was associated with improved hemoglobin, decreased rHuEPO dose, and decreased resistance to rHuEPO. Muscle function, exercise capacity, myocardial function, and arrhythmia, could not be reliably assessed because of the non-combinable nature of end points and the limited number of trials [21]. In the present study, the most common reason for starting carnitine was musculoskeletal problems. In muscle, there is no synthesis but uptake and storage of carnitine, and some studies in hemodialysis patients have reported improvements in exercise capacity, muscle weakness, and cramps, after the administration of carnitine [22].

The results of this study must be interpreted in light of the following limitations. First, it was retrospective and the patients were not randomized to receive carnitine therapy. In an attempt to overcome this shortcoming, a paired analysis comparing hospitalization and hospital day rates before and after carnitine administration in the same patients was performed. This strategy was also used to address the issue of confounding by indication, which means that patients who took carnitine were likely selected because they were sicker. By using the same patients as their own controls, the possible bias associated with selecting appropriate controls was eliminated. Second, the lower rates of hospitalization observed in the carnitine period could reflect a regression to the mean effect. To test this issue, hospitalization rates in cases (those who took carnitine) and controls (those who did not take carnitine) were compared. The cases were pair-matched to controls by age, gender, race, diabetes status, year of initiation of dialysis, total duration of dialysis and overall hospitalization rates during the entire time at risk. The finding in the case-control analysis of steady hospitaliza-

tion rates in the controls and declining rates after the initiation of carnitine therapy in the cases argues against a regression to the mean effect. Third, the lower hospitalization rates that were observed in the carnitine period could reflect survival bias. However, in the first 6 months of the carnitine period, when follow-up of patients was complete, there was a statistically significant reduction in the hospitalization and hospital day rates. Also, the effect of time on dialysis prior to initiation of carnitine was accounted for in the multivariate model. Moreover, the finding in the case-control analysis of similar death rates in both groups makes survival bias unlikely. Fourth, cardiovascular comorbidity is likely to be underestimated because the only source for this information was hospitalizations for cardiovascular disease. Lastly, prescribing differences of carnitine therapy could not be assessed because of the retrospective nature of the study.

Despite these limitations, our study demonstrates an association between carnitine therapy and lower hospital utilization among hemodialysis patients. Given the high cost associated with hospitalizations, the potential impact of carnitine therapy in dialysis patients deserves further investigation. An adequately powered randomized clinical trial that takes into account potential confounders could provide a final answer to this question. It could also help to solve existing controversies regarding the effects of carnitine and to identify potential subsets of patients who might benefit from this therapy.

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