L-Carnitine Supplementation for the Treatment of Fatigue and Depressed Mood in Cancer Patients with Carnitine Deficiency

A Preliminary Analysis

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ABSTRACT: Nutritional factors are among the postulated causes of fatigue, a highly prevalent symptom in the cancer population, with serious impact on patients' quality of life. Deficiency of the micronutrient carnitine may play a role by reducing energy production through fatty acid oxidation. We present preliminary data of an open-label, dose-finding study to determine safety and maximally tolerated dose (MTD) of 1 week of L-carnitine supplementation in cancer patients with fatigue and carnitine deficiency. Patients who met inclusion/exclusion criteria underwent carnitine level determination. Eighty-three percent of these patients (15/18) had carnitine deficiency. Preliminary data analysis of 13 patients showed that total carnitine increased from 30.0 ± 6.9 to 41.0 ± 12.1 (mean ± SD) after 1 week of supplementation ($P = 0.01$), and free carnitine increased from 24.3 ± 6.1 to 33.8 ± 9.8 ($P = 0.004$). Outcome measures were fatigue (BFI score), depression (CES-D), sleep disruption (ESS), and performance status (Karnofsky). Median (min, max) BFI score at baseline was 73 (46, 82) versus 50 (3, 82) after 1-week supplementation ($P = 0.009$). CES-D score at baseline was 29 (16, 42) and 22 (8, 32) after 1 week ($P = 0.028$). ESS at baseline was 46.5 (0, 69) and 30.4 (0, 72) after 1 week ($P = 0.015$). Karnofsky score did not change significantly ($P = 0.38$). We are currently conducting a randomized, double-blind, placebo-controlled study to rigorously assess the role of L-carnitine for the treatment of fatigue and depression in cancer patients.

KEYWORDS: L-carnitine; supplementation; cancer patients; fatigue; depression; carnitine deficiency

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INTRODUCTION

Cancer patients often complain of a myriad of symptoms that may be caused either by the disease or by the treatment itself.[1–4] It has become apparent that fatigue, a highly prevalent symptom in this patient population, is frequently underdiagnosed and undertreated, and has a serious impact on quality of life.[1,4] Fatigue is a condition associated with asthenia, malaise, and lethargy, and is characterized by decreased mental capacity and energy.[1,2] A survey of 419 cancer patients found that 79% complained of daily fatigue that interferes with their daily activities,[3] while a similar survey,[5] conducted in ovarian cancer patients, showed a prevalence of 60%. While anemia, electrolyte imbalance, and centrally acting drugs have been extensively studied as factors leading to fatigue,[1,2] the role of micronutrients, which play a key role in energy metabolism and detoxification, has been minimally explored.

Most of the body's energy is stored as fat (85%), primarily in the form of triglycerides (TG), and only 0.5% is stored as complex carbohydrates.[6,7] During prolonged periods of fasting, exercise, stress, or illness, large amounts of free fatty acids (FFA) are released from TG. Consequently, FFA become the preferential source of energy for most tissues requiring high levels of energy, such as cardiac and skeletal muscle. Thus, the body makes optimal use of its most abundant energy source, fat in the form of TG, without compromising its structural integrity. Yet, the efficiency of fatty acid metabolism is critically dependent on a single cofactor, carnitine.[6,7]

Carnitine, a micronutrient found in meat and dairy products, is a short-chain nitrogen-containing carboxylic acid that plays a key role in energy metabolism. It mediates the transport of long- chain fatty acids across the inner mitochondrial membrane, facilitates the β-oxidation of fatty acids, and regulates the intracellular ratio of free/acyl CoA, thus regulating ATP formation. Carnitine also has important mitochondrial detoxification properties.[6,7] Impaired mitochondrial energy production, β-oxidation, and detoxification lead to critical metabolic inefficiency and mitochondrial dysfunction. The protective effect of carnitine on mitochondrial metabolism has been extensively documented in experimental models.

Patients with cancer are especially at risk for carnitine deficiency. They frequently present with decreased caloric intake and increased metabolic requirements. In addition, numerous medications can interfere with the absorption, synthesis, and excretion of carnitine. In particular, chemotherapy with ifosfamide and cisplatin-based agents may result in increased urinary carnitine excretion and serum carnitine deficiency because they compete with carnitine reabsorption at the proximal convoluted tubule.

Early studies by Winter *et al*. reported carnitine deficiency in 50% of patients with chronic illness, including cancer.[8] Shortly after, Dodson *et al*. observed a significant decrement in L-carnitine levels in 23 cancer patients compared to 13 healthy age-matched controls.[9] Esteban-Cruciani *et al*. reported that 63% of pediatric patients with chronic illness and fatigue had carnitine deficiency.[10,11] We observed that 67% (30/45) of adult-hospice-cancer patients with fatigue had carnitine deficiency (Cruciani *et al*., personal communication). Graziano and coworkers observed improvement of fatigue with L-carnitine supplementation in 44 out of 55 nonanemic cancer patients with cisplatin-based, chemotherapy-induced, carnitine deficiency.[12] In addition, carnitine administration prevents cardiomyopathy induced by doxorubicin[13] and interleukin-2.[14]

We present here a preliminary analysis of a dose-finding safety study for L-carnitine replacement in cancer patients with a life expectancy of less than 6 months. These data suggest a role for L-carnitine supplementation in the treatment of fatigue and depressed mood in patients with cancer.

METHODS

Study Population

The study was approved by the Institutional Review Board, Beth Israel Medical Center, New York, NY. Cancer patients were recruited from the Jacob Perlow Hospice and the Cancer Center at Beth Israel Medical Center. Inclusion criteria were as follows: 18 years or older; diagnosis of cancer and more than 3 months of life expectancy; self-report of moderate to severe fatigue for at least a week prior to accrual; carnitine deficiency; and Karnofsky score ≥ 50. The exclusion criteria were as follows: severe lung, cardiac, or renal disease; brain tumor; stroke; inability to complete the assessment tools due to language barriers; initiation of erythropoietin treatment less than 3 months prior to accrual; radiation or chemotherapy within 1 week prior to accrual; changes in mental status that would interfere with participation in the study; and inability to consent for the study. Carnitine levels (total and free) were measured both at baseline and at the end of 1 week of L-carnitine supplementation by a radioenzymatic assay (Quest Laboratories).[15] Acylcarnitine was calculated by subtraction of free from total carnitine. Carnitine deficiency was defined as free carnitine < 35 μmol/L for males and < 25 μmol/L for females (normal range of 35–67 and 25–55, respectively), or a ratio[8] of acylcarnitine (total − free)/free carnitine > 0.4.

Study Design

A standard up-down dose-finding design was utilized to determine the maximum tolerated dose (MTD) of L-carnitine given by mouth in carnitine-deficient cancer patients with fatigue. The design called for 3 patients to be enrolled at each dose level. The beginning dose was 250 mg/day, with doses increased in increments of 500 mg to a maximum target dose of 3000 mg/day.

Outcome Measures

Fatigue (measured by the Brief Fatigue Inventory, BFI),[16] depressed mood (Center for Epidemiological Studies Depression Scale, CES-D),[17] quality of sleep (Epworth Sleeplessness Scale, ESS),[18] and performance status (Karnofsky Performance Status)[19] were assessed at baseline and after 1 week of L-carnitine supplementation. All the instruments utilized in the study have been validated.

Statistical Analysis

Descriptive statistics are presented as the mean ± SD for normally distributed variables (e.g., age) and as the median (minimum, maximum) for skewed data (e.g., BFI). Standard errors for median values were estimated using the jackknife

method.[20] Pre/post-comparisons were done using either a Student's paired *t* test or a Wilcoxon nonparametric test for paired data. An intent-to-treat (ITT) approach was used, and all subjects who had pre- and post-test data were included for analysis even if they were considered to be protocol violators. All analyses were carried out using SPSS 11.5 (SPSS Inc., Chicago, IL).

RESULTS

A total of 645 patients were approached between December 2002 and April 2004. Of these, only 3% met inclusion criteria and consented to participate in the study. The reasons for noninclusion in the study are illustrated in FIGURE 1. The primary causes were being too ill (30%), still receiving radiation/chemotherapy (22%), changes in mental status (11%), and diagnosis of brain tumor (8%). Eighteen patients satisfied preliminary criteria for carnitine deficiency, and 15 of these were carnitine-deficient (83%) based on laboratory confirmation.

Three patients were to be enrolled at each dose level. The beginning dose was 250 mg/day, with doses increased in increments of 500 mg to a maximum target dose of 3000 mg/day. To date, 15 patients have been recruited into the study. Of these, 13 completed all measures, while 2 patients dropped out before completion of L-carnitine supplementation (one on 750 and one on 1750 mg/day). Three patients completed 250, 750, and 1250 mg/day. Four patients were recruited into the 1750 mg/day group due to 2 patients' protocol violations (use of illicit drugs and opioid-induced changes in mental status). These 2 patients were still included in the pre/post-data analysis. No adverse events related to L-carnitine were reported for any patient.

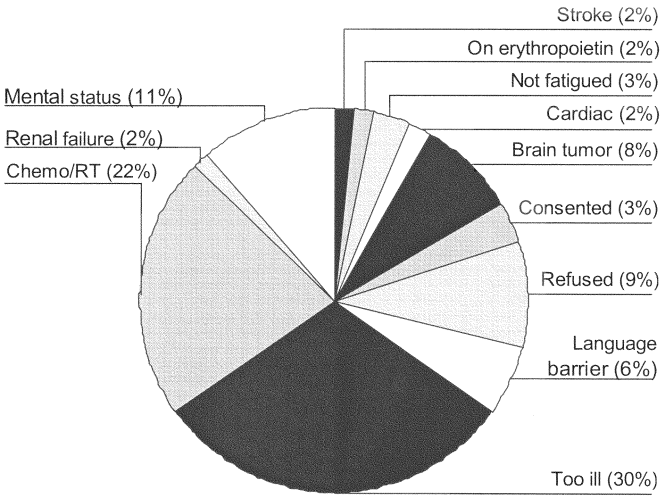

FIGURE 1. Patients screened for the study (n = 645 patients).

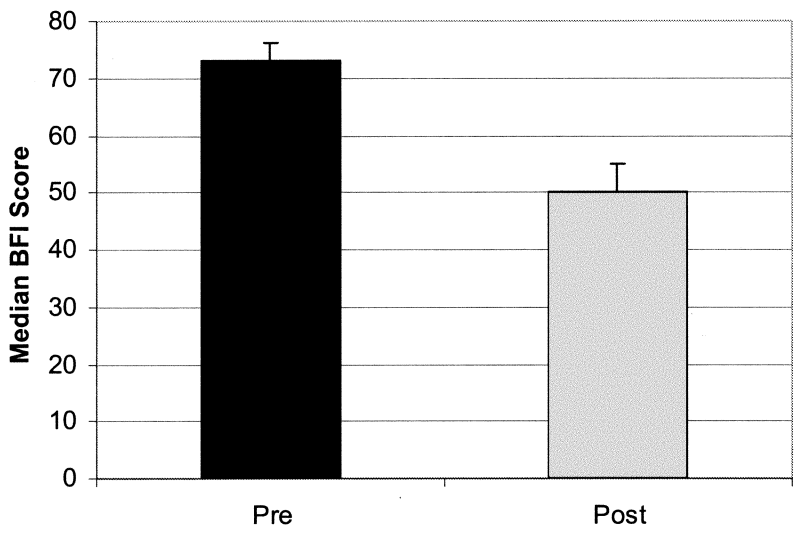

FIGURE 2. Effect of L-carnitine supplementation on fatigue. Comparisons of BFI scores before and after L-carnitine supplementation. Fatigue was assessed utilizing the BFI.[16] Standard errors for median values were estimated using the jackknife method.[20] Pre/post-comparisons were done using either a Student's paired *t* test or a Wilcoxon nonparametric test for paired data.

Of the 13 patients included in the ITT analysis, 6 were female, and mean ± SD age was 55 ± 11 years. The two largest cancer diagnosis groups were breast (33%) and colorectal (25%). Preliminary analysis showed that the mean ± SD total L-carnitine increased from 30.0 ± 6.9 to 41.0 ± 12.1) after 1 week of supplementation ($P = 0.01$), and free L-carnitine increased from 24.3 ± 6.1 to 33.8 ± 9.8 ($P = 0.004$). Analysis by gender showed that females had significantly lower levels of total (females, 24.8 ± 7.1; males, 34.4 ± 2.0; $P = 0.005$) and free L-carnitine (females, 19.5 ± 4.8; males, 28.4 ± 3.4; $P = 0.002$) at baseline, but there were no significant differences after 1 week of supplementation. As shown in FIGURE 2, median (min, max) BFI score at baseline was 73 (46, 82) versus 50 (3, 82) after 1 week ($P = 0.009$). Median (min, max) CES-D at baseline was 31.3 (16, 48) and 22.0 (6, 40) after 1 week ($P = 0.028$; see FIG. 3). Median (min, max) ESS at baseline was 17.5 (0, 24) and 8 (0, 15) after 1 week ($P = 0.015$; see FIG. 4). Median Karnofsky score did not change significantly ($P = 0.38$).

DISCUSSION

The prevalence of carnitine deficiency in patients with cancer and self-reported symptoms of fatigue was extremely high (83%). Our study suggests that L-carnitine supplementation is safe up to 1750 mg/day in these patients and may have beneficial effects on symptoms of fatigue, depression, and quality of sleep in cancer patients

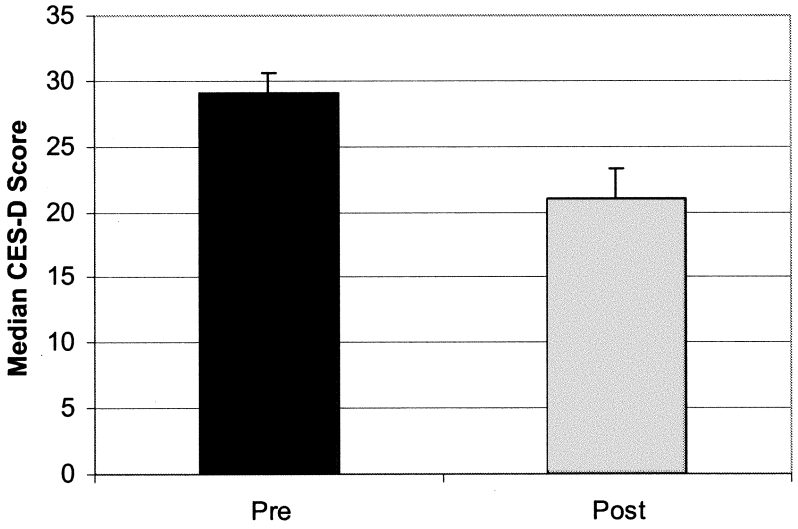

FIGURE 3. Effect of L-carnitine supplementation on mood. Comparisons of CES-D scores before and after L-carnitine supplementation. Depressed mood was measured by CES-D.[17] Standard errors for median values were estimated using the jackknife method.[20] Pre/post-comparisons were done using a Wilcoxon nonparametric test for paired data.

with carnitine deficiency. Remarkably, a significant improvement in patients' symptoms was observed after only 1 week of L-carnitine supplementation. This rapid response is consistent with the study by Graziano *et al.* who observed improvement in fatigue scores in cancer patients undergoing cisplatin- and ifosfamide-based chemotherapy after only 1 week of L-carnitine supplementation.[12] Also, a rapid response was reported in children with AIDS and fatigue after L-carnitine supplementation.[10] We observed almost a 40% increase in free-carnitine serum levels ($P = 0.004$) at the end of the 1-week study period. Previous studies have shown that changes in the plasma free-carnitine pool readily correlate with changes in the muscle compartment.[21]

Systemic carnitine depletion has been described as secondary to a variety of metabolic disorders and is characterized by fatigue, muscle weakness, decreased tolerance to metabolic stress, and cardiomyopathy. Carnitine plays a key role in intracellular energy metabolism and detoxification.[7] Consequently, it is reasonable to hypothesize that carnitine deficiency, which was highly prevalent in our study population, contributed to the symptoms of fatigue observed in cancer patients. This finding is consistent with the studies by Winter *et al.* and Esteban-Cruciani *et al.*, who also observed a high prevalence of carnitine deficiency in patients with chronic illness (including cancer) and fatigue.[8,10,11] Similarly, Dodson *et al.* reported a significant decrement in carnitine levels in cancer patients compared to healthy controls.[9] The etiology of carnitine deficiency in patients with cancer is likely to be multifaceted, including decreased caloric intake, impaired absorption, and increased metabolic requirements. In addition, numerous medications can interfere with the absorption, synthesis, and excretion of carnitine.[7]

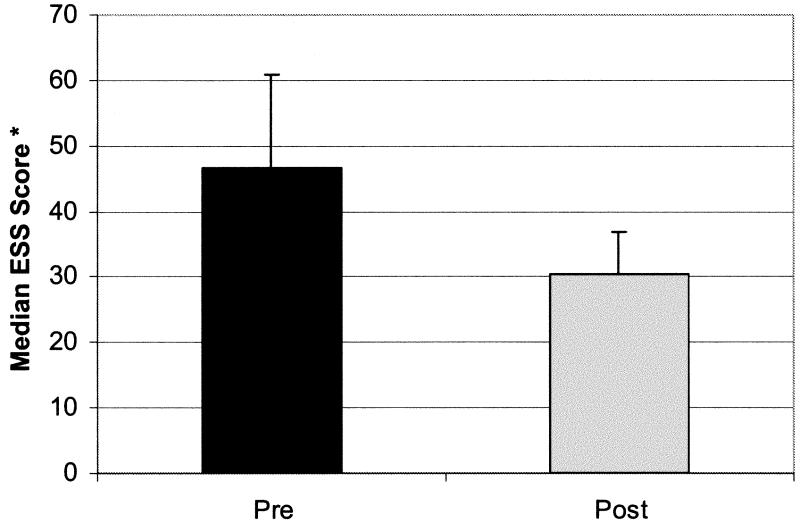

FIGURE 4. Effect of L-carnitine supplementation on sleep. Comparisons of ESS scores before and after L-carnitine supplementation. *Based on a maximum possible score = 100%. Quality of sleep was assessed by ESS.[18] Standard errors for median values were estimated using the jackknife method.[20] Pre/post-comparisons were done using either a Student's paired *t* test or a Wilcoxon nonparametric test for paired data.

The low accrual rate observed is not surprising in this patient population. Most patients were referrals from hospice who typically have a survival rate of less than 45 days. In addition, they have multiple medical problems, including large changes in mental status. Our protocol excluded patients undergoing radiation or chemotherapy, which constrained the number of patients eligible for the study even more.

The present study provides some interesting findings. First, it highlights the high prevalence of carnitine deficiency (83%) in patients with cancer reporting moderate to severe fatigue, suggesting that this is a very important and frequent medical problem. Second, it indicates that blood levels can be restored with only 1 week of supplementation, although it is unlikely that muscle compartment levels were fully restored by the end of the study. Third, even low doses of L-carnitine supplementation may have an impact on fatigue, mood, and quality of sleep in cancer patients.

This preliminary analysis has some limitations, and the conclusions should be taken with caution. This is an open-label study and there is the possibility of a placebo effect. Our strict inclusion and exclusion criteria, as well as the low accrual rate, may limit generalizability of the results. In addition, the study was designed for 7 doses (21 patients), but the results of the only 4 doses available to date are reported here. Furthermore, we cannot comment on the potential effect of higher L-carnitine doses or prolonged treatment on patients' symptoms. Based on previous studies, we can contemplate that muscle stores were partially restored during the 1-week period; however, we cannot speculate as to whether the results observed were primarily due to skeletal muscle or central nervous system effects. Finally, we did not monitor

patients' dietary carnitine intake, which may possibly have contributed to increased data variability.

Although a major concern is the possibility that L-carnitine supplementation may accelerate cancer progression or interfere with the chemotherapeutic effect of certain agents, the current body of evidence suggests the opposite.[22] It has been shown that L-carnitine has a protective effect on adriamycin-induced toxicity without interfering with antitumor activity or promoting tumor growth.[22] Pretreatment with L-carnitine actually increased the survival time and did not affect adriamycin inhibition of leukemic colony formation in mice.[23] In addition, L-carnitine supplementation did not promote osteosarcoma growth or mammary carcinoma in mice. Finally, *in vitro* studies have shown that the adriamycin effect is not affected by preincubation with carnitine in pancreatic tumor cell lines.[22]

Together, these findings point toward a role for L-carnitine supplementation in the treatment of fatigue and depression in patients with cancer and provide the conceptual framework for the design of clinical trials using oral L-carnitine as a simple, well-tolerated therapeutic strategy.

We are currently conducting a randomized, double-blind, placebo-controlled study to rigorously assess the role of L-carnitine for the treatment of fatigue and depression in cancer patients.

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