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Beneficial Effects of L-Carnitine in Dialysis Patients with Impaired Left Ventricular Function: An Observational Study

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SUMMARY

Background: Recent studies have shown that L-carnitine may improve clinical status and reduce the need for erythropoietin in dialysis patients with cardiovascular diseases. In this observational study, we investigated whether the addition of L-carnitine to conventional therapy might improve cardiac function (as assessed by M-mode and two-dimensional echocardiography) and clinical status in dialysis patients with left ventricular dysfunction.

Methods: Eleven dialysis patients with reduced left ventricular function (EF < 45%) were treated with L-carnitine for 8 months. Two-dimensional (2-D) echocardiography was performed at baseline and every 2 months up to the end of the treatment period. The dosage of erythropoietin was also monitored during the study and the patients' clinical status was assessed by a questionnaire.

Results: Carnitine increased mean LV ejection fraction from 32.0% to 41.8% ($p < 0.05$ vs baseline). There was also a slight reduction of erythropoietin dosage and an improvement of clinical status.

Conclusions: Eight months' therapy with carnitine appears to improve LV function and clinical status in dialysis patients with impaired LVF.

Introduction

Numerous studies have investigated the effects of haemodialysis on carnitine metabolism. Although impaired renal function is associated with decreased clearance, and thus elevated plasma levels of carnitine, uraemic patients undergoing dialysis generally exhibit a relative carnitine deficiency characterised by subnormal plasma concentrations of free carnitine and depleted muscle stores, whereas plasma levels of carnitine esters (acylcarnitines) are abnormally elevated. The loss of carnitine through the dialysis membrane appears, therefore, to be compensated by a shift of this compound from tissue stores into plasma, with redistribution from free carnitine to acylcarnitine[1–4]. In fact, patients undergoing dialysis often exhibit normal concentrations of total carnitine[4–6]. Recently, a pharmacokinetic study in long-term haemodialysed patients has confirmed that there is a substantial removal of L-carnitine and L-acetyl-carnitine by haemodialysis, and that repeated intravenous administration of L-carnitine at each dialysis session increases both predialysis and postdialysis concentrations of this compound, suggesting that the plasma accumulation of L-carnitine induced by treatment is due to replenishment of the deep tissue pool[7].

Cardiovascular disease is a common finding in dialysis patients, accounting for 40% of deaths in this population. In this regard, congestive heart failure (CHF) in chronic haemodialysis patients,

particularly when associated with dilated cardiomyopathy, represents an ominous complication and is an independent risk factor for cardiac mortality[8,9]. The relationship between carnitine levels and cardiac function in patients with end-stage renal disease has not been fully clarified. However, subnormal levels of free carnitine have been reported in patients with ischaemic heart disease or heart failure, and an inverse correlation has been observed between plasma free carnitine levels and cardiothoracic ratio[10–12]. Furthermore, there appears to be a significant association between low free carnitine levels and reduced ejection fraction[13].

There is evidence that carnitine supplementation is beneficial in the treatment or prevention of many clinical conditions seen in dialysis patients and may also reduce the need for erythropoietin[1,14–17]. Also, recent studies have shown an improvement in survival and/or cardiac function upon administration of L-carnitine in patients with heart failure or acute myocardial infarction (MI)[18,19].

The aim of this study was to investigate whether the addition of L-carnitine to conventional therapy might be associated with beneficial effects on cardiac function and clinical status in dialysis patients with impaired left ventricular function (LVF).

Patients and Methods

Twenty-three patients (20 men, 3 women) with uraemia on periodic haemodialysis (three times a week) underwent echocardiographic assessment and 11 had signs of impaired LVF (EF < 45%). After a run-in period of 1 month, during which the stability of the LVF measurements was assessed, these patients were started on L-carnitine 1 g intravenously during each dialysis session and the treatment was continued for 8 months. Two-dimensional (2-D) echocardiography was performed at baseline and every 2 months up to the end of the treatment period. The assessment was performed in all patients on the day after dialysis (between 24 and 30 h after completion of the dialysis session), with the subjects positioned in left lateral decubitus.

All statistical parameters were calculated as mean ± standard deviation. One-way analysis of variance was used for overall significance. The significance of changes over time and between groups at each time point was assessed by the Newman–Keul test after the samples were tested for normal distribution. A value of $p < 0.05$ was considered significant.

Results

Clinical characteristics of the study patients are listed in Table 1. Eight patients had a history of ischaemic heart disease (defined as a documented history of myocardial infarction [MI], typical angina, an exercise electrocardiogram positive for ischaemia, or angiographic evidence of coronary disease) and two had a history of arterial hypertension. Six out of 11 patients were symptomatic for heart failure (New York Heart Association [NYHA] functional class II to III). All patients were treated with digitalis and ten patients were also receiving angiotensin-converting enzyme (ACE) inhibitors.

The main changes in left ventricular ejection fraction (LVEF) during carnitine treatment are shown in Figure 1. A progressive improvement in mean LVF was observed, with significant increases already apparent after 2 months of treatment. Heart rate, systolic and diastolic BP values remained unchanged. The clinical status of the patients, assessed by NYHA functional class, improved slightly during the treatment period. Similarly, a slight but important decrease in the dosage of erythropoietin from 7000 (±3000 SD) UI to 6000 (±2000 SD) UI was recorded.

Table 1. *Clinical characteristics of the study patients (n = 11)*

Age (years)	63 ± 10
Men/women	10/1
Duration of dialysis (months)	20 ± 17
Heart rate (beats/min)	73 ± 12
Systolic blood pressure (mmHg)	135 ± 9
Diastolic blood pressure (mmHg)	78 ± 7
Current treatment:	
ACE inhibitors (%)	10
digitalis (%)	11
nitrates (%)	2
NYHA classification:	
I (%)	5
II (%)	4
III (%)	2

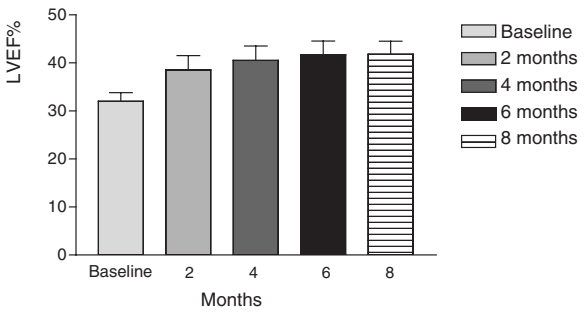

Figure 1. *Changes in left ventricular ejection fraction (LVEF; %) during L-carnitine treatment (11 patients)*

Discussion

These data demonstrate that an 8-month treatment period with L-carnitine, 3 g/week administered parenterally, can improve cardiac function and the clinical status of dialysis patients with LV dysfunction. The time-course of LV functional changes in this study was evaluated by means of 2-D echocardiography. A significant improvement in LVEF was evident after 2 months and progressively increased until the end of the trial.

Only a few studies have investigated so far the potential role of L-carnitine in patients with cardiac dysfunction. Our results confirm the main findings of previous investigations regarding the beneficial effects of L-carnitine supplementation in such patients. Similar to what was observed in post-MI patients in the CEDIM trial, we observed an improvement of LV function after L-carnitine treatment. In the CEDIM trial, a significant reduction of both end-diastolic and end-systolic volumes was found in L-carnitine vs. placebo recipients 1 year post-MI, however no significant changes were observed in LVEF[19]. A significant increase in LVEF vs. baseline was found in a randomised, placebo-controlled study conducted in 50 patients with LV dysfunction who received 6 months' treatment with L-propionylcarnitine[20]. In a recently published placebo-controlled study conducted in 80 patients with heart failure caused by dilated cardiomyopathy, long-term L-carnitine administration resulted in a significantly decreased mortality rate compared with placebo (3 vs 18%) over a 3-year period[18]. The results of studies investigating the effects of carnitine supplementation on LV function in haemodialysis patients are more controversial. In an open-label study conducted with 16 patients on haemodialysis who underwent a 3-month treatment with L-carnitine, a significant increase in LVEF vs baseline was found in the subgroup of patients with lower ejection fraction[13]. Three months of L-carnitine supplementation failed to improve cardiac function in 13 carnitine-deficient, haemodialysed children, while no LVEF changes were found in two short-term studies in haemodialysed adults, although other indices of cardiac functions showed improvements[21–23]. Taken together, these data suggest that a long duration of carnitine treatment may be necessary to obtain an improvement in cardiac function, and that positive results are more easily observed in patients with clinically evident cardiac dysfunction[1].

It is well known that carnitine is an essential cofactor in myocardial metabolism since it regulates the transport of long-chain fatty acids from the cytoplasm into mitochondria, where fatty acids are oxidised to produce ATP, the primary source of energy for the heart. Recent research suggests that carnitine also regulates the enzymes that control the balance between carbohydrate and lipid metabolism[24]. There is increasing evidence that the main pathogenetic mechanisms leading to cardiac hypertrophy and, ultimately, heart failure, may be triggered by a forced reduction of cardiac utilisation of fatty acids[25]. Many factors may have contributed to the improvement in LV function observed in our study, i.e. correction of carnitine deficiency secondary to chronic haemodialysis, normalisation of lipid profiles and/or optimisation of fatty acid metabolism within the heart.

There are limitations inherent in an observational study, such as failure to take into account any placebo effect or time effects, lack of randomisation and controls, and investigators' potential bias. Furthermore, our study involved a fairly small and heterogeneous group of patients. Nevertheless, these data suggest that L-carnitine may be an important addition in the pharmacological management of dialysis patients, not only for its beneficial effect on LFV, but also for the sparing effect on erythropoietin. Future controlled studies are needed to confirm these observations and survival studies are needed to evaluate whether the beneficial effects observed in this study may eventually translate into decreased mortality in dialysis patients with impaired LVF.

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