INTRODUCTION

Cardiac dysfunction remains the major cause of mortality and morbidity in hemodialysis patients. Hemodialysis patients have many risk factors for cardiac diseases including hypertension, hypoalbuminemia, hyperlipidemia, hyperhomocysteinemia, anemia, oxidative stress of uremia and dialysis, elevated C-reactive protein, arteriovenous fistula and coronary artery and valvular calcifications. Recurrent volume overload, accumulation of advanced glycation end products, ventricular hypertrophy, and deficit of metabolically essential substances for myocardial cell also have been suggested as potential contributors to the cardiac dysfunction in these patients. Moreover, patients with normal ventricular function during long-term hemodialysis may have arrhythmia, exercise intolerance, and unexplained cardiac hypertrophy.

Deficiency of carnitine has been implicated in the pathogenesis of cardiac morbidities and left ventricle dysfunction in hemodialysis patients. Carnitine is necessary for transport of long chain fatty acids from the cytoplasm to the mitochondrial matrix for their β-oxidation in the myocardium. An additional role of carnitine is the release of mitochondrial coenzyme A (CoA) from acyl-CoA when the free CoA supply is limited due to the accumulation of metabolites of β-oxidation within the mitochondrion.

Several studies revealed that L-carnitine declines constantly during dialysis and that its plasma level is inversely correlated with time on dialysis. The possible causes of this decline are postulated to be the reduced dietary intake of L-carnitine, impaired biosynthesis or transport of L-carnitine, and loss of L-carnitine from the body by hemodialysis. Few studies with conflicting results have been performed to demonstrate the cardioprotective effects of L-carnitine in hemodialysis patients.

The aim of this study was to evaluate the effects of exogenous L-carnitine supplementation on the heart-related symptoms, signs, and electrocardiographic findings in the long-term hemodialysis patients with normal or poor cardiac function.

MATERIALS AND METHODS

We prospectively studied 12 randomly selected chronic hemodialysis patients (mean age, 47.9 y; female:made
ratio, 1:3) from the dialysis center at the university hospital (Tabriz, Iran) from December 2001 and September 2002. The exclusion criteria included a history of coronary artery disease or a known secondary cardiomyopathy, recent changes in the cardiac medications, or invasive cardiac procedures such as a coronary bypass grafting, a percutaneous coronary angioplasty, or a pacemaker placement. The patients had, on average, 32.0 months of dialysis before enrollment to this study. The patients were on hemodialysis 2 times per week, each lasted 4 hours. L-carnitine (500 mg/day orally) was initiated for a period of 6 months while continuing their regular hemodialysis. The patients were on iron supplement, erythropoietin, folate, and calcium carbonate for at least 3 months before the study. Ten out of 12 patients (83%) received either angiotensin-converting enzyme inhibitor or atenolol for their hypertension. No major changes were allowed on the drug chart of the patients during the study period.

The patients were examined for cardiac symptoms such as dyspnea, orthopnea, chest pain in addition to the cardiac functional class (New York Heart Association classification). We followed the cardiac signs including cardiac sounds, murmurs, and arrhythmias before carnitine administration (baseline, 0 month) and monthly, thereafter, up to 6 months. Two-dimensional echocardiographic parameters (using GE Wingmed CFM 800 SV echocardiography machine) including left ventricular ejection fraction (left ventricular EF, end-diastolic and end-systolic volumes and left ventricular mass were recorded at the beginning of the study and after 6 months. Left ventricular mass was estimated from M-mode dimensions of septal thickness, posterior wall thickness, and left ventricular internal dimensions at end-diastole.

Hematocrit and hemoglobin levels of all the patients were also measured at 0, 1, 2 and 3 months of L-carnitine supplementation.

**Statistical Analyses**

All data were expressed as means ± SD. Statistical analyses were performed with SPSS software for Windows (Statistical Product and Service Solutions, version 11.0, SSPS Inc, Chicago, IL, USA). Values for \( P \) less than .05 were considered significantly positive.

**RESULTS**

Five of 12 patients (41%) had congestive heart failure with functional class (FC) III that improved to FC II, I, and asymptomatic state in 2, 1 and 2, respectively, at 6 months (Figure 1). This improvement was noted within 2 to 4 months of L-carnitine supplementation. Four out of 5 patients (80%) with congestive heart failure had paroxysmal nocturnal dyspnea, which disappeared by 2 (in 3 patients) and 4 (in 1 patient) months of therapy. Systolic murmur resolved their murmurs by the second month of treatment. Two out of 4 patients (50%) with murmur of grade III/VI improved their grades to II/VI by the first month of treatment. A third heart sound that was audible in 2 patients disappeared in one patient by the end of 6 months.

One patient had recurrent 10 premature ventricular contractions per minute detected on initial electrocardiogram. They reduced to 2 premature ventricular contractions per minute by 3 months of L-carnitine therapy and remained at this frequency up to the end of the study.

Eight out of 12 patients (66%) had left ventricular ejection fraction less than 60% before study; the mean left ventricular ejection fraction was 43.8% ± 9.54% that improved to 54.8% ± 8.56% at 6 months (\( P < .05 \)). Two patients with the lowest baseline left ventricular ejection fraction (about 30%) showed the most significant improvement (up to 100% increase) in their left ventricular ejection fraction after 6 and left ventricular mass did not change significantly at 6 months of treatment with carnitine (Figures 3 and 4). Finally, a significant improvement was noted in the mean hemoglo-
bin 8.78 ± 0.52, 9.23 ± 0.39, 9.36 ± 0.40, and 9.93 ± 0.44 g/dL after 1, 2, and 3 months of L-carnitine administration, respectively (P = .002).

DISCUSSION

Cardiovascular disease is a significant cause of morbidity and accounts for as many as 50% of deaths in dialysis patients.1, 13 The US National Kidney Foundation Task Force on Cardiovascular Diseases targeted coronary artery disease and left ventricular hypertrophy as the potential methods of reducing cardiovascular mortality in patients with chronic renal diseases.5 They noted that even in maintenance hemodialysis patients with normal cardiac function, myocardial fatty acid metabolism is disrupted, and L-carnitine administration can restore normalcy.5

The results of our study showed that L-carnitine intake caused a remarkable improvement in the cardiac function of chronic hemodialysis patients without significant changes in the left ventricular mass and end-diastolic volume. Most of the observed improvements in the cardiac signs and symptoms as well as the electrocardiographic findings occurred early at 2 to 4 months of treatment with the L-carnitine. The reduction in the intensity of cardiac murmur could be the result of improved flow dynamics due to improvement of myocardial function. The hematocrit and hemoglobin levels also increased steadily after the initiation of L-carnitine. However, these levels were still within the anemia-range at 3 months and alone could barely explain the observed benefits of L-carnitine supplementation on the cardiac parameters of chronic hemodialysis patients.

Sakurabayashi and associates,8 Fagher and associates,14 and Topagloglu and associates15 found no improvement in the myocardial performance after 6 to 8 weeks and 3 months of L-carnitine supplementation, respectively. Conversely, Matsumoto and associates (1990) noted a better left ventricular function after 6 to 18 months of treatment.7 Our study showed that left ventricular ejection fraction increased by 6 months of L-carnitine administration. This suggests the prolonged duration of intake required for normalization of fatty acid metabolism in the myocardium.

Chronic hemodialysis patients with severe cardiomyopathy may improve with L-carnitine therapy.8 Matsumoto and associates postulated that hemodialysis patients with more-depressed cardiac function were more likely to respond to L-carnitine intake.1 Our results also show that 2 of our patients with the least baseline left ventricular ejection fraction had the most pronounced improvement (up to 100%) in their ventricular functions.

Left ventricular hypertrophy was documented even in the earlier stage of renal failure,16, 17 and carnitine deficiency was an independent cause of cardiomegaly.10 In 1 study, a 20% reduction in left ventricular mass (measured by MRI) was noted after 6 months of L-carnitine therapy.7 Our echocardiographic findings did not show any substantial change in left ventricular mass after L-carnitine administration. When patients with left ventricular mass with higher baseline value were evaluated separately, reduction at 6 months though numerically high was not statistically significant. This possibly is due to the small number of patients in our study, and therefore needs a larger study to
clearly show the benefit of carnitine supplementation in this population.

In conclusion, L-carnitine supplementation may improve subjective and objective manifestations of cardiac dysfunction in chronic hemodialysis patients; however, a larger study is needed to validate these findings.

REFERENCES


