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Effects of L-Carnitine Supplementation on Cardiac Morbidity in Hemodialyzed Patients

: Matsumoto, Yoshihiro; Sato, Motoyoshi; Ohashi, Hiroshige; Araki, Hajime; Tadokoro, Mitsunobu; .

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(English): Cardiac diseases are well known among patients on maintenance hemodialysis (HD), and carnitine deficiency may be an important factor in cardiac morbidity. We studied the effects of low-dose L-carnitine treatment (500mg/day) on chest symptoms (dyspnea on exertion, chest pain, palpitation), cardiac function, and left ventricular (LV) mass in 9 HD patients with reduced ejection fraction (EF). After 6 months of L-carnitine treatment, most patients had at least some improvement in chest symptoms, while LVEF was increased and LV mass was decreased. Carnitine fractions increased and reached plateaus at 2-3 times the baseline levels. These results suggest that prolonged low-dose L-carnitine treatment can improve the cardiac morbidity by restoring decreased carnitine tissue levels and impaired oxidation of FFA. Copyright [copy 2000 S. Karger AG, Basel

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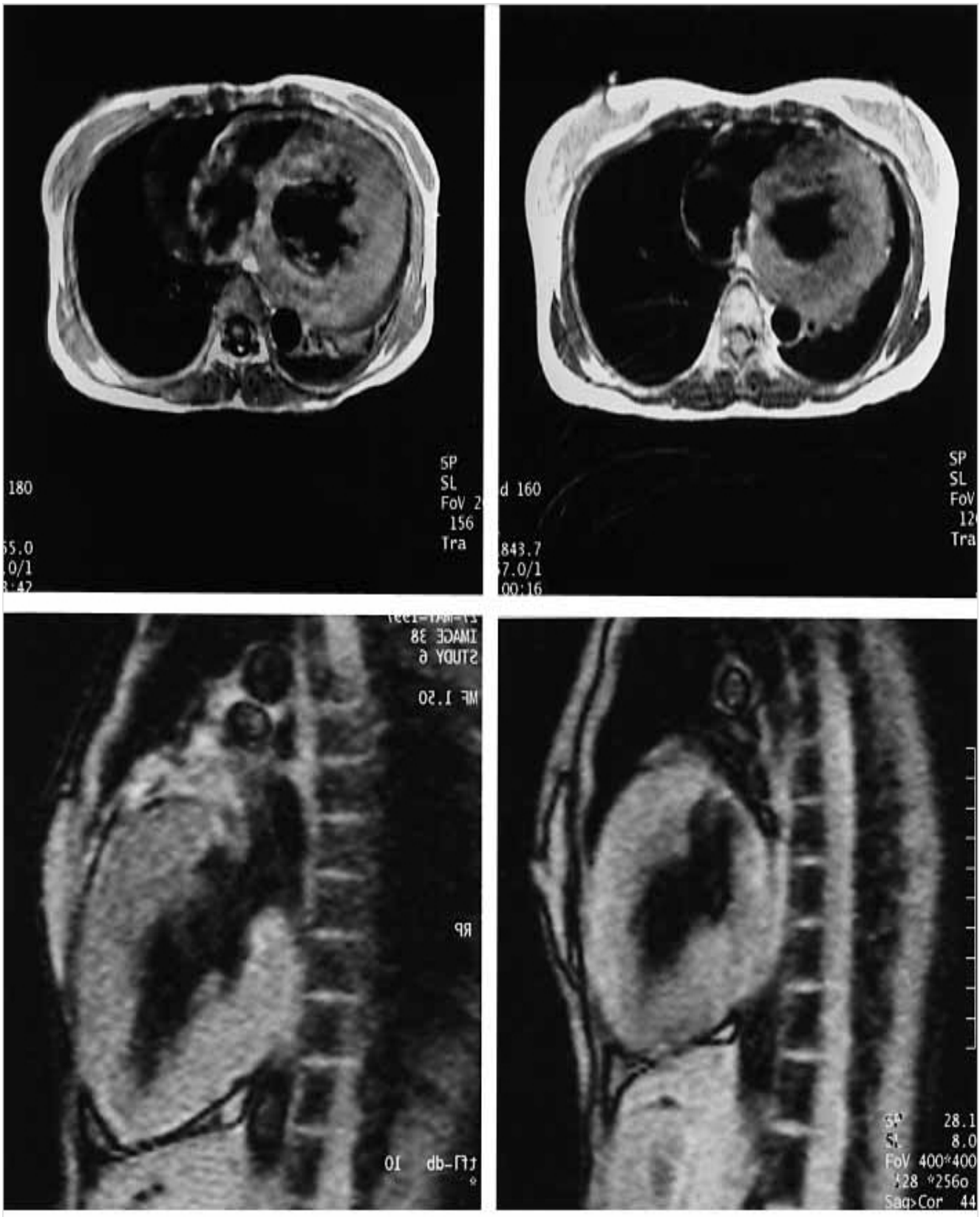

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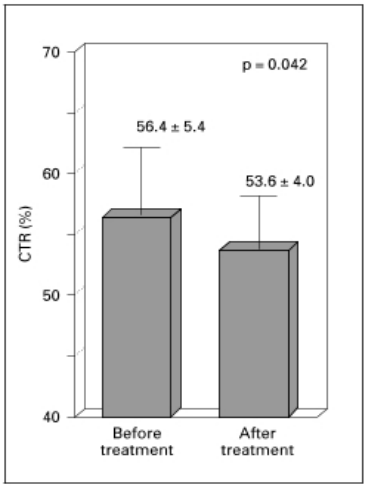
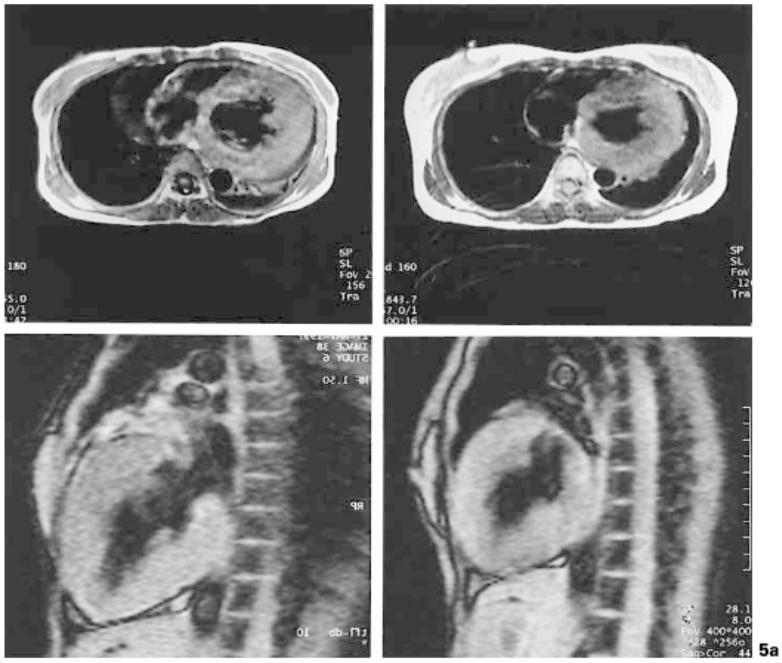


Fig. 3. Effects of *L*-carnitine supplementation on cardiothoracic ratio (CTR). Chest X-ray films were evaluated immediately before dialysis. The figure shows means ± SD of CTR before and after the study.



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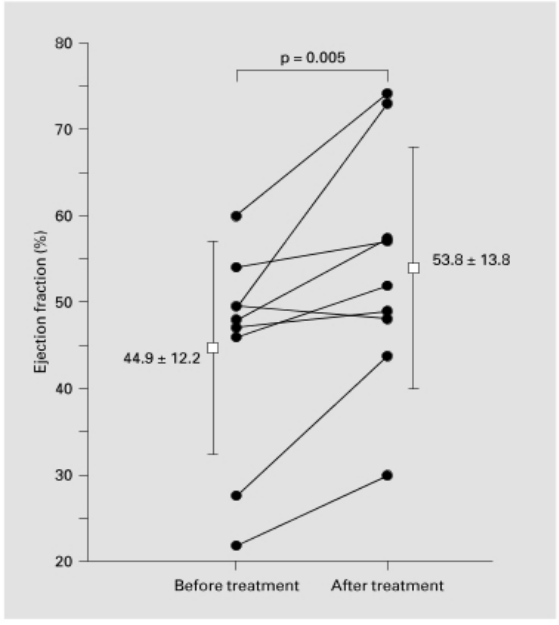

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showed poor response to erythropoietin of 9,000 U/week regardless of their adequate serum iron and ferritin levels. Hematocrit levels of some patients remained under 30% because of hypertension or frequent obstruction of blood access. Seven of the 9 patients were hypertensive, and were well controlled receiving antihypertensive agents such as β-blocker or angiotensin-converting enzyme inhibitor.

Effect of Oral L-*Carnitine Treatment on Cardiogenic Symptoms*

Each patient with dyspnea on exertion, palpitation and chest pain was given *L*-carnitine (500 mg/day orally) for 6 months. During the course of the study, *L*-carnitine treatment positively affected 11 of 13 symptoms in 9 patients (fig. 1). No patient showed adverse effects during *L*-carnitine treatment.

Fig. 4. Effects of *L*-carnitine supplementation on LVEF. Each patient received gated blood pool scintigraphy on nondialysis days. The figure shows means ± SD of LVEF before and after treatment.

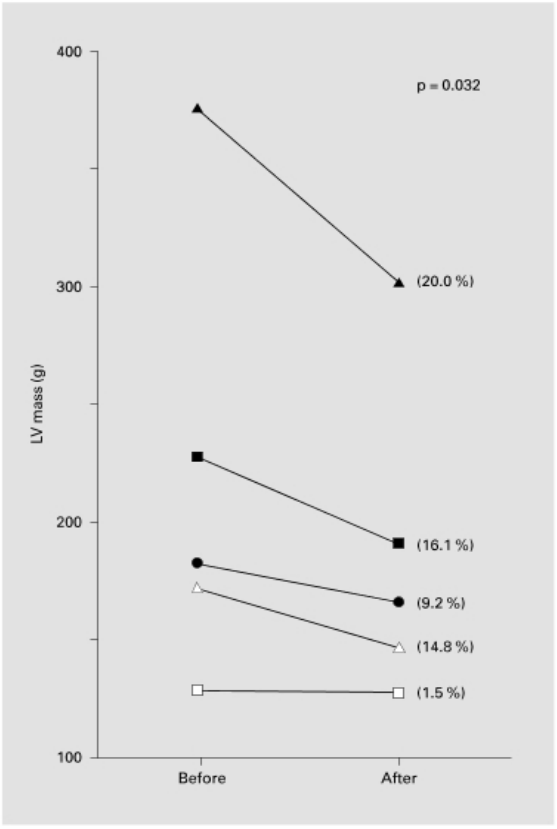

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Fig. 5. Effects of *L*-carnitine supplementation on LV mass by using MRI. **a** Dramatic reduction of LV mass during treatment in a 32-year-old female who had been on HD for 7 years. Her primary disease was Alport's syndrome. Upper, end-systolic axial view; lower, end-systolic sagittal view crossing interventricular septum. **b** Changes in LV mass during *L*-carnitine treatment in each of 5 randomly selected patients. LV mass after treatment was reduced significantly compared with that before treatment. The numbers indicate reduction rates in LV mass during treatment.

Effect of Oral L-*Carnitine Treatment on Carnitine Fraction Concentration*

Predialysis values of FC, AC, TC and AC/FC ratio during *L*-carnitine treatment are shown in figure 2. At the start of the study, the mean FC was lower, TC was borderline, and AC was normal as compared to the normal ranges. After 3 months of *L*-carnitine treatment, the mean values of serum TC, FC and AC had increased to 2–3 times the baseline levels, and they remained at plateaus until the end of the study. AC/FC ratio was also determined, because an AC/FC ratio of >0.25 suggests a free carnitine insufficiency [18]. The AC/FC ratio, which showed markedly elevated levels at the start of the study, decreased toward normal after 3 months of treatment, corresponding to previous data [10].

Effect of Oral L-*Carnitine Treatment on Cardiothoracic Ratio (CTR)*

To evaluate the effect of the treatment on patients' heart size, CTR was examined on chest films immediately before dialysis. As shown in figure 3, mean CTR after treatment was significantly suppressed compared to that before treatment (from 56.4 ± 5.4% to 53.6 ± 4.0%). Since postdialysis body weight was constant during the study and no significant difference was found in predialysis body weight before and after *L*-carnitine treatment, the observed improvement of cardiomegaly was thought not to be due to change of total blood volume.

Effect of Oral L-*Carnitine Treatment on Reduced LVEF*

To assess the effect of *L*-carnitine treatment on cardiac function, LVEF was examined by gated blood pool scintigraphy performed before and after treatment on nondialysis days. Reduced mean LVEF at the start of treatment was significantly improved after 6 months (fig. 4, from 44.9 ± 12.2% to 53.8 ± 13.8%).

Effect of Oral L-*Carnitine Treatment on Enlarged LV Mass*

To determine whether *L*-carnitine treatment affects cardiac muscle mass, LV mass was measured by MRI with ECG gating in 5 randomly selected patients, this technique being more accurate and reproducible than M-mode echocardiography [19, 20]. A representative case is shown in figure 5a. Significant enlarged LV mass before treatment was reduced by 20% after treatment. Similar results seemed to be obtained with other patients (fig. 5b).

Discussion

It is now possible to classify carnitine deficiency into two categories. A primary genetic carnitine deficiency occurs in children with dilated cardiomyopathy, hypoglycemia, and low carnitine contents in plasma, liver and muscle, owing to a defect in a common high-affinity trans-

Several studies have shown that HD patients exhibit a constant loss of plasma carnitine through filtration and that subsequent endogenous biosynthesis does not sufficiently restore plasma carnitine to basal levels [7–9]. Recently it was reported that plasma-free carnitine deficiency was correlated with time on dialysis [10]. Böhmer et al. [8] found that the muscle carnitine content after dialysis in HD patients was only 10% of normal controls. Kudoh et al. [11] suggested that carnitine deficiency was involved in the pathogenesis of cardiomegaly. Against this background, some groups [10, 12, 13] have reported beneficial effects of oral supplementation of high-dose (2 g/day) or low-dose (0.5 g/day) *L*-carnitine on dialysis-associated muscle symptoms. Suzuki et al. [14] showed that the incidence of arrhythmias during HD were significantly reduced by oral *L*-carnitine supplementation. However, an echocardiographic test showed no effects of *L*-carnitine on left ventricular (LV) function [15].

In the current study, to examine the involvement of carnitine depletion in the pathogenesis of cardiac morbidity in HD patients, we evaluated the effect of *L*-carnitine supplementation on LV hypertrophy and reduced LV function by highly accurate approaches.

Materials and Methods

Patients

Nine patients from three participating centers with end-stage renal disease of varying causes were selected for *L*-carnitine treatment study. All patients had been on maintenance HD three times weekly (4 h each dialysis) for more than 3 years. They were experiencing some chest symptoms that may have been cardiogenic, and showed significantly reduced LVEF in echocardiography. All patients had signs of LV hypertrophy, but showed no arrhythmias in their electrocardiograms before dialysis. They were taking standard medications, including calcitriol, vitamin D_3, calcium carbonate, and erythropoietin. Their HD therapy was characterized by ultrafiltration control, bicarbonate base, cellulose, or cellulose acetate membranes. Throughout the carnitine treatment study, postdialysis body weight, drug regimens, and diet remained unchanged. Informed consent was obtained from each patient.

Design of L-*Carnitine Treatment Study*

Before the start of the *L*-carnitine treatment, all patients received blood tests including serum carnitine fraction, chest radiographs, and gated blood pool scintigraphy for baseline determination. These patients were then given a daily dose of 500 mg oral *L*-carnitine each morning on nondialysis days or after dialysis treatment for 6 months. *L*-Carnitine USP (500 mg vanilla-flavored chewable wafers) was purchased from Vitaline Corp. (USA). The routine laboratory assessment and chest radiographs were repeated monthly. The change of serum carnitine status was assessed every 3 months. Pool scintigraphy was repeated 6 months after initiation of treatment. Each patient was questioned about the chest symptoms every 3 months. Five of the 9 patients were randomly selected for magnetic resonance imaging to determine LV mass at the start and the end of the study.

Table 1. Patients' characteristics[1]

Patients	9
Male/female	2/7
Age, years	62.1 ± 16.9
Duration on dialysis, months	107 ± 54
Primary cause of ESRD	
Glomerulonephritis	6
Diabetes	2
Alport's syndrome	1
CTR, %	56.4 ± 5.4
Ejection fraction, %	44.9 ± 12.2
Hematocrit, %	28.0 ± 3.9
Total cholesterol, mg/dl	178 ± 32
Triglyceride, mg/dl	94 ± 51

[1] Continuous variables are expressed as mean ± SD.

Serum Carnitine Assay

Blood samples were collected immediately before HD. Serum carnitine profiles (free carnitine (FC), acyl carnitine (AC), and total carnitine (TC)) were determined at the Bio-Medical Laboratory (Tokyo, Japan), based on the method described by Deufel [16]. Normal values for serum FC, AC and TC were 36–74, 6–23 and 45–91 μmol/l, respectively.

Assessment of Clinical Status

During the study, special attention was given to symptomatology. The 9 patients had experienced chest symptoms for at least 3 months. As a control period, we observed the symptoms in each patient for the last 2 week before the start of the carnitine treatment. We found no evident change in the symptoms in this period. Each patient was interviewed every 3 months by a physician, who was blinded as to the purpose of the study and recorded the intensity of dyspnea on exertion, palpitation and chest pain. The severity of symptoms was scored as 0, no symptoms; 1, slight; 2, moderate and 3, severe. The scores were based on the frequency, intensity and duration of the symptoms during and between HD treatments in each patient. The interviewing physician was the same for the entire duration of the study.

Gated Blood Pool Scintigraphy

All patients received gated blood pool scintigraphy on nondialysis days. It was performed with human serum albumin labeled with 20 mCi of technetium-99m. A high-sensitivity Anger camera (Starcam 4000iXR/T, GE Yokogawa Medical System) was employed in a modified left anterior oblique position. A total of 5 million counts were acquired for each study. The LVEF was calculated from the raw data curves using standard software.

Magnetic Resonance Imaging (MRI)

Five of the 9 HD patients were randomly selected to receive MRI before and after *L*-carnitine treatment. This was performed at 1.5 T

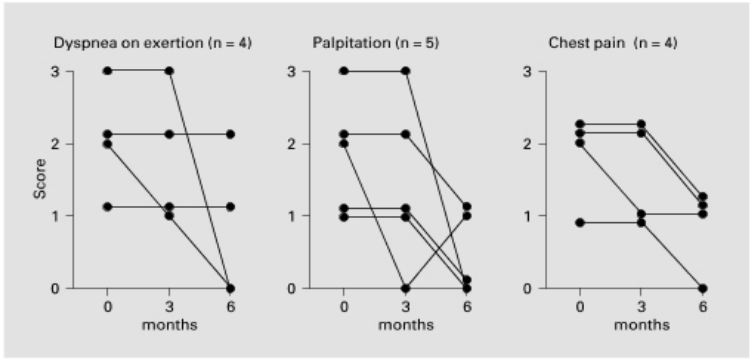


Fig. 1. Improvement in chest symptoms (dyspnea on exertion, chest pain and palpitation) by oral *L*-carnitine supplementation. The severity of each symptom was scaled as described in Materials and Methods. During the course of treatment, 85% of 13 symptoms in 9 patients were improved to some extent.

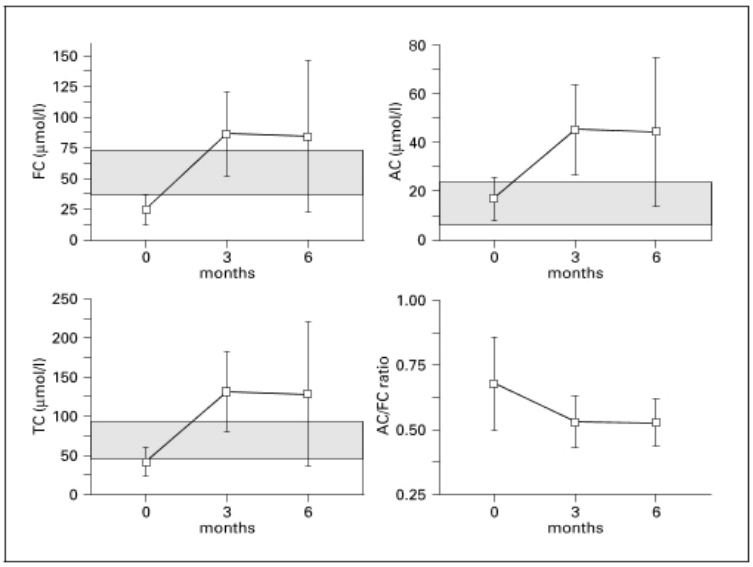


Fig. 2. Effects of *L*-carnitine supplementation on free carnitine (FC), acyl carnitine (AC), total carnitine (TC) and AC/FC ratio. Normal ranges for FC, AC and TC are indicated by shaded areas. The figure shows means ± SD of each set of patient data.

by using the standard head coil of a Siemens Magnetom Vision MR scanner (Siemens AG, Erlangen, Germany). The spin-echo images are obtained using an ECG gating. For cardiac cine, a matrix of 128 × 256 at two excitations yields an acquisition time of 256 cardiac cycles with the ECG gating. To determine the LV mass, images obtained from cardiac imaging were evaluated using the Argus software (Siemens Inc.) [17].

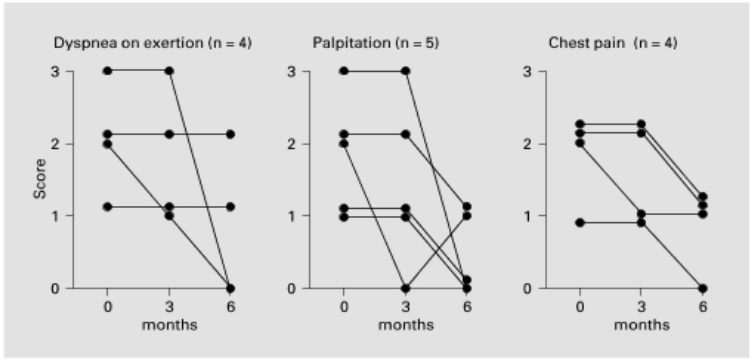
Statistical Analysis

The results were expressed as means ± SD. Student's t test was used to evaluate statistical significance for paired data. Values of $p < 0.05$ were considered statistically significant.

Results

Patients' Characteristics

The main clinical and biological characteristics of the patients, at the start of the treatment, are summarized in table 1. Nine patients (2 males and 7 females) aged 32–84 years (mean 62) were included. Glomerulonephritis was the main primary nephropathy. Duration of dialysis was 44–216 months (mean 107). Interdialytic body weight change was 2.7–8.7% (mean 6.0%), and Kt/V, which indicates dialysis volume, was 1.40–2.05 (mean 1.66). The mean hematocrit value was 28.0 ± 3.9%. Some patients



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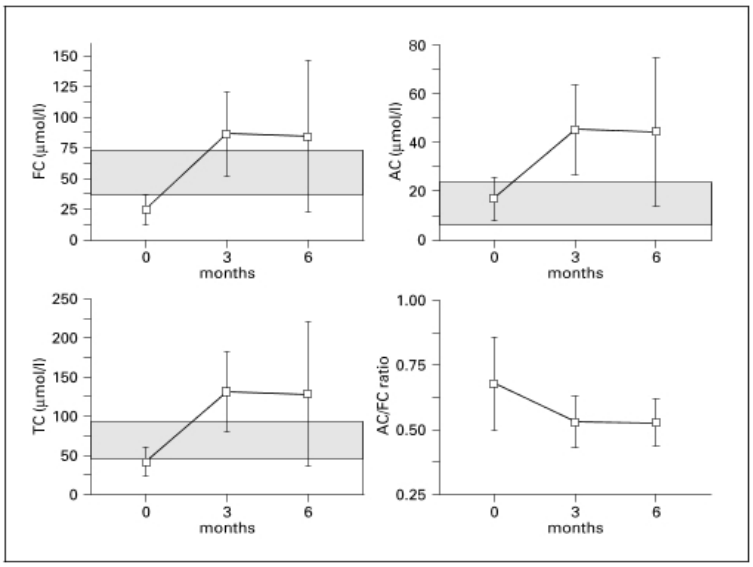

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