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Improvement of Myocardial Fatty Acid Metabolism through *L*-Carnitine Administration to Chronic Hemodialysis Patients

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Key Words

L-Carnitine · Myocardial fatty acid metabolism · Chronic renal failure · Hemodialysis · ^{123}I-Labeled β-methyl-*p*-iodophenyl-pentadecanoic acid

Abstract

The concentration of carnitine, which is essential to fatty acid metabolism, can decrease markedly in patients on long-term hemodialysis coincident with life-threatening cardiac damage. However, administration of *L*-carnitine improves the myocardial function of these patients. To evaluate the underlying events of this phenomenon, we used recently developed technology, ^{123}I-labeled β-methyl-*p*-iodophenyl-pentadecanoic acid (BMIPP) myocardial scintigraphy, as a test of myocardial fatty acid metabolism. Our results showed that the free carnitine concentration (19.2 ± 6.5 μmol/l) was lower in 11 chronically dialyzed patients than in 8 healthy controls (49.3 ± 7.7 μmol/l, $p < 0.0001$). Additionally the heart to mediastinal ratio (H/M) of BMIPP was higher for these patients than for the controls (1.91 ± 0.19 vs. 1.52 ± 0.24, $p < 0.005$), and the patients' washout rate (WOR) of BMIPP was lower (17.2 ± 6.0 vs. 22.8 ± 4.2%, $p < 0.05$). After *L*-carnitine was administered orally to the patients at doses of 1 g/day for 1 month and 0.5 g/day for the following month, the concentration of free carnitine in their sera increased to 85.4 ± 27.0 μmol/l ($p < 0.0001$). Although the H/M ratio did not change (1.89 ± 0.20) with this treatment, their WOR increased to 21.9 ± 6.6% ($p < 0.001$), similar to that of controls. The left ventricular end-diastolic dimension and left ventricular fractional shortening remained unchanged, as shown by echocardiography. The results presented here denote that a carnitine deficiency in chronically hemodialyzed patients disrupts their myocardial fatty acid metabolism, which is improved by *L*-carnitine supplementation.

Introduction

Cardiac damage is a common complication of uremia in patients undergoing long-term hemodialysis [1]. Pathogenic mechanisms that could cause the high prevalence of left ventricular abnormalities in these patients include

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cardiac overload (anemia, overhydration, and hypertension), coronary artery disease, hyperparathyroidism, and carnitine deficiency [2].

Carnitine is absolutely required for the transport of long-chain fatty acids from the cytoplasm into the matrix of mitochondria, the site of β-oxidation [3]. Additionally, carnitine is essential for the tissues' use of fatty acids for energy production, especially such tissues as the skeletal muscle and myocardium [4]. Consequently, a carnitine deficiency in neonates leads to severe congestive heart failure, a condition that is alleviated by *L*-carnitine administration [5]. In chronically hemodialyzed patients, *L*-carnitine supplementation reduces the incidence of cardiac arrhythmias [6] and improves cardiac function [7]. Hypocarnitinemia is a risk factor of cardiomegaly in such patients [8]. Golper and Ahmad [9] described 2 patients on long-term hemodialysis with severe cardiomyopathy who unexpectedly displayed low levels of carnitine until treatment with *L*-carnitine subsequently improved their cardiac function [9]. Amounts of serum free carnitine are significantly lower in hemodialysis patients than in healthy persons, and this decrease bears a positive correlation to the concentration of tissue carnitine [10]. Yet the possible relationship between physiological impairment and the effect of carnitine deficiency on myocardial fatty acid metabolism in hemodialysis patients has not been studied in detail.

A newly established method for examining myocardial fatty acid metabolism is ^{123}I-labeled β-methyl-*p*-iodophenyl-pentadecanoic acid (BMIPP) myocardial scintigraphy [11]. To clarify whether a carnitine deficiency affects myocardial fatty acid metabolism in chronically dialyzed patients and, if so, whether carnitine supplementation is beneficial, we evaluated these patients using BMIPP scintigraphy. Cardiac function was monitored by echocardiography before and after carnitine administration and compared that of healthy volunteers used as controls.

Materials and Methods

Subjects

Participants in this study were 11 ambulatory patients (8 men and 3 women) receiving hemodialysis for periods of 11–30 (mean duration 21.1 ± 6.8) years. All were stable and underwent 4–5 h of intermittent hemodialysis three times a week. Patients with histories of diabetes mellitus, prior myocardial infarction, or valvular heart disease were excluded. Patients' ages ranged from 46 to 73 (mean 60.7 ± 8.5) years. Controls were 8 adults without renal or heart disease (5 men and 3 women, mean age 62.3 ± 9.4 years). All 19 subjects signed informed consent forms before entering this study.

Study Design

At time zero (T0), we recorded baseline values for general laboratory measurements, complete hemograms, and lipid profiles. Serum total carnitine, free carnitine and acylcarnitine concentrations were determined by the enzymatic cycling method [12] in patients and controls.

L-Carnitine (Vitaline Co., Oakdale, Calif., USA) was administered at 1 g/day orally for 1 month and then at 0.5 g/day for the following month. Two months later (T2), the same humoral laboratory parameters and carnitine were measured.

Echocardiography and BMIPP Myocardial Scintigraphy

Echocardiography and BMIPP myocardial scintigraphy of the patients were conducted on the day between hemodialysis treatments at T0 and T2. Echocardiography was prepared using an SSD-870 system (Aloka, Tokyo, Japan). For each subject, the left ventricular end-diastolic dimension (LVEDD), left ventricular fractional shortening (LVFS), interventricular septal wall thickness (IVS) and left ventricular posterior wall thickness (PW) were also measured.

On the days of myocardial imaging, the patients fasted until after the late images were obtained. During patients' rest periods, they were injected intravenously with 111 MBq of BMIPP. Twenty minutes later, the early images were acquired by using a ZLC 7500 gamma camera (Siemens, Solna, Sweden). Anterior planar images were obtained first; then the camera was rotated more than 180° from the 45° right anterior oblique to the 45° left posterior oblique position to obtain single photon emission computer tomography (SPECT) images. Thirty-two images were obtained at 25 s/image in a 64 × 64 matrix on a nuclear medicine computer (Scintipac 70A, Shimazu, Kyoto, Japan). There were no attenuation or scatter corrections. A 20% window was centered at the 159 KeV photo peak of ^{123}I. Late imaging was carried out 4 h after injection by repeating the same imaging procedure as for early imaging.

On planar images, cardiac and mediastinal regions of interests were located manually, and counts per pixel were determined in each region. To minimize background effects, the heart to mediastinal ratio (H/M) for early images was calculated for evaluation of myocardial BMIPP uptake; then the washout rate (WOR) was found for each matrix of the SPECT images to compute myocardial BMIPP clearance.

Echocardiography and BMIPP myocardial scintigraphy were also performed on controls, after which H/M and WOR of BMIPP were calculated by the same method used for patients.

Statistical Analysis

All results are expressed as means ± SD and analyzed with Student's t test for paired or unpaired samples. Correlations were found by linear regression (Pearson's r). A p value of < 0.05 was considered significant.

Results

Carnitine Concentration (table 1)

In control subjects the serum total carnitine concentration was 47.6–71.0 (mean 58.9 ± 8.6) μmol/l, whereas free carnitine measured 39.8–62.2 (mean 49.3 ± 7.7) μmol/l, and the acylcarnitine to free carnitine ratio

Table 1. Laboratory parameters of the patients before (T0) and after (T2) carnitine supplementation (mean ± SD)

	T0	T2
Total carnitine, μmol/l	35.3 ± 11.9	137.6 ± 37.9**
Free carnitine, μmol/l	19.2 ± 6.5	85.4 ± 27.0**
Acylcarnitine to free carnitine ratio	0.87 ± 0.25	0.64 ± 0.15*
Albumin, g/dl	4.22 ± 0.38	4.16 ± 0.30
Total cholesterol, mg/dl	203.6 ± 52.3	197.0 ± 48.3
Triglyceride, mg/dl	126.0 ± 74.4	121.8 ± 77.7
HDL cholesterol, mg/dl	54.9 ± 14.9	55.1 ± 13.1
Free fatty acid, mEq/l	0.32 ± 0.15	0.22 ± 0.12
Hematocrit, %	30.6 ± 5.6	30.1 ± 4.6
Kt/V	1.39 ± 0.34	1.45 ± 0.36

* $p < 0.01$ vs. T0. ** $p < 0.0001$ vs. T0.

Table 2. Echocardiographic parameters of the patients before (T0) and after (T2) carnitine supplementation compared with normal controls (mean ± SD)

	Controls	T0	T2
LVEDD, mm	49.3 ± 5.2	48.8 ± 5.3	47.1 ± 5.9
LVFS, %	37.5 ± 4.9	33.8 ± 7.3	32.8 ± 6.8
IVS, mm	8.8 ± 0.9	10.5 ± 1.5*	10.6 ± 1.9*
PW, mm	8.3 ± 1.3	10.2 ± 1.3**	10.8 ± 1.8**

LVEDD = Left ventricular end-diastolic dimension; LVFS = left ventricular fractional shortening; IVS = interventricular septal wall thickness; PW = left ventricular posterior wall thickness.

* $p < 0.05$ vs. controls. ** $p < 0.01$ vs. controls.

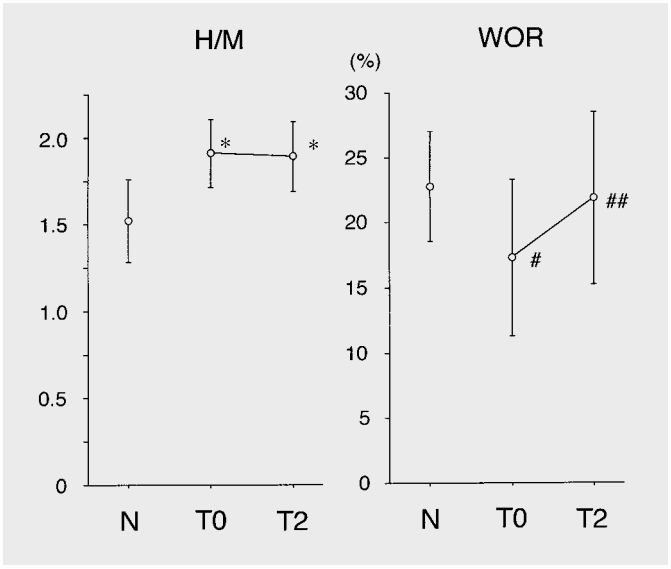

Fig. 1. Results of BMIPP myocardial scintigraphy of patients before (T0) and after (T2) carnitine supplementation compared with normal controls (N). Data are expressed as means ± SD. H/M = Heart to mediastinal ratio; WOR = washout rate. * $p < 0.005$ vs. N; # $p < 0.05$ vs. N; ## $p < 0.001$ vs. T0.

was 0.11–0.35 (mean 0.20 ± 0.07). Comparatively, in chronically dialyzed patients at T0, the pretreatment baseline, total carnitine, free carnitine and acylcarnitine to free carnitine ratio were 35.3 ± 11.9 and 19.2 ± 6.5 μmol/l, and 0.87 ± 0.25, respectively. Therefore, the content of total carnitine and free carnitine at T0 was significantly lower in patients than in the controls ($p < 0.0005$, $p < 0.0001$). Moreover, all patients at T0 had less free carnitine than the controls' minimum value. The acylcarnitine to free carnitine ratio in patients at T0 exceeded that in controls ($p < 0.0001$). Neither serum total carnitine, free carnitine, nor the acylcarnitine to free carnitine ratio correlated with patients' ages or duration of hemodialysis in this study (data are not shown).

At T2, i.e., after 2 months of *L*-carnitine supplementation, the content of total carnitine and free carnitine increased significantly to 137.6 ± 37.9 and 85.4 ± 27.0 μmol/l, respectively ($p < 0.0001$, $p < 0.0001$) in the patients, and concentrations of both factors exceeded those of controls ($p < 0.0001$, $p < 0.005$). The acylcarnitine to free carnitine ratio decreased significantly to 0.64 ± 0.15 ($p < 0.01$). Still, the acylcarnitine to free carnitine ratio remained higher than in controls ($p < 0.0001$).

Laboratory Measurements (table 1)

In 8 of 11 patients given constant erythropoietin supplements, hematocrit increased from 28.1 ± 4.6 at T0 to 30.3 ± 5.4% at T2 ($p < 0.05$). Because the other 3 patients' hematocrit values were >35% during the study period, their erythropoietin supplement was reduced. As a consequence, their hematocrit values decreased from 37.0 ± 1.0 at T0 to 29.7 ± 2.3% at T2. The amounts of free fatty acid decreased from 0.32 ± 0.15 at T0 to 0.22 ± 0.12 mEq/l at T2, but not to a significant extent. All other laboratory parameters showed essentially equal values. The frequency and extent of dialysis treatment were also basically the same for all patients.

BMIPP Myocardial Scintigraphy (fig. 1)

H/M established by scintigraphy of these patients was 1.91 ± 0.19 at T0 and higher than that of controls (1.52 ±

0.24, $p < 0.005$). Conversely, the scintigraphic WOR for our patients was 17.2 ± 6.0% at T0 and lower than for controls (22.8 ± 4.2%, $p < 0.05$). Neither the patients' H/M nor WOR correlated with their age or duration of hemodialysis (data are not shown). We therefore combined the latter two indices in the remaining calculations. At T2 H/M did not change (1.89 ± 0.20) and was still higher than that of controls ($p < 0.005$). However, the WOR increased significantly to 21.9 ± 6.6% at T2 ($p < 0.001$), eventually equaling that of the controls.

Echocardiography (table 2)

At T0 the patients had no left ventricular dilatation, as indicated by their LVEDD, compared to healthy controls. Similarly, the patients' LVFS was 33.8 ± 7.3%, which was as good as that of controls. However, the left ventricular walls of patients were thickened, measurements referred to here as IVS and PW, with values of 10.5 ± 1.5 and 10.2 ± 1.3 mm, respectively. The echocardiographic parameters did not change after carnitine supplementation.

Discussion

When comparing the WORs of BMIPP before and after *L*-carnitine supplementation of uremic patients, we found that this treatment increased and normalized their defective myocardial fatty acid metabolism as their deficiency of serum free carnitine dissipated. The basis of this test procedure is that the free fatty acid analogue, BMIPP, when absorbed into the myocardium, forms BMIPP-CoA for use in the synthesis of triglyceride or oxidation. BMIPP-CoA must be metabolized via α-oxidation to permit the resulting α-methyl product to undergo cycles of β-oxidation and is favorable for imaging because it is metabolized over longer time periods than free fatty acids. Fujibayashi et al. [13] found that pretreatment with tetradecylglycidic acid, a mitochondrial carnitine acyltransferase I inhibitor, increased the accumulation and prolonged the retention of BMIPP in the myocardium. Thus myocardial washout of BMIPP depends on the activity of a carnitine shuttle. When Kropp et al. [14] examined myocardial fatty acid metabolism with ^{123}I-iodophenyl-pentadecanoic acid, differences in early and late tissue tracer activity became evident. Taking these properties into consideration, we adapted BMIPP scintigraphy to measure the BMIPP WOR as an indicator of myocardial fatty acid metabolism.

Before *L*-carnitine supplementation, serum free carnitine concentrations of all the chronically dialyzed patients tested here were below the lowest value of healthy controls. Since tissue and plasma free carnitine concentrations correlate [10], it was only natural for the myocardial free carnitine content of these patients to have decreased. After *L*-carnitine supplementation, serum free carnitine concentrations increased above those in controls. Undoubtedly myocardial carnitine did so at the same time. This presumption is based on a demonstration of increased and normalized muscle free carnitine concentrations during 60 days of oral *L*-carnitine administration [15]. In our study, myocardial fatty acid metabolism reached normalcy after *L*-carnitine treatment, enabling us to conclude that disturbance of this function was responsible for carnitine deficiency in these patients. Clearly, carnitine deficiency that disrupts this metabolic process could cause eventual heart failure or cardiac arrhythmia in chronically hemodialyzed patients, conditions that should be offset by carnitine supplementation.

The uptake of BMIPP, indicated by H/M, is dependent on the ATP content of myocardial cytosol [13], the number of myocardial cells, and the rate of coronary blood flow. Before *L*-carnitine supplementation of our patients, their H/M ratio was higher than in healthy controls. Accordingly, we speculated that the patients' myocardial ATP content had not decreased in spite of their carnitine deficiency, and that the back diffusion of BMIPP did not accelerate, although the enhanced thickening of these patients' left ventricular wall might have increased the H/M ratio. In recipients of long-term hemodialysis, the functions disrupted by a lack of carnitine activity apparently make free fatty acids remain for long periods in the cytoplasm, although myocardial uptake of fatty acid is preserved.

Before treatment with *L*-carnitine, the patients had normal left ventricular function on echocardiograms obtained during rest intervals between dialysis treatments, although their myocardial fatty acid metabolism was disrupted. Several explanations are possible. The ventricular function may have been maintained by energy that the adult heart can generate from glucose metabolism as well as fatty acid metabolism. Additionally, ventricular function might remain intact even in the face of a carnitine deficiency, which is not as extensive in adults as neonates [5], whose condition can be severe enough to cause congestive heart failure. Cardiac stress tests, which were not done here, might have detected some dysfunction in these patients that was not otherwise apparent. Finally, even patients with normal left ventricular systolic function during long-

term hemodialysis may develop a disruption in myocardial fatty acid metabolism followed by arrhythmia, poor exercise tolerance, and unexplained cardiac hypertrophy.

Our echocardiographic findings indicated that LVEDD and LVFS did not change after *L*-carnitine administration. Such stability in LVFS is consistent with the finding that the H/M ratio, an indicator of myocardial ATP content, was unchanged by supplementation. Fagher et al. [16] similarly found that myocardial performance did not improve during 6 weeks of *L*-carnitine supplement, yet Khoss et al. [7] noted better left ventricular function after 6–18 months of carnitine treatment, a result that we could not confirm. As with 'myocardial chronic stunning' [17] in which the restoration of left ventricular wall motion is delayed following their improvement in blood flow, considerable time may be required for improvement in myocardial performance subsequent to normalization of myocardial fatty acid metabolism.

Thus, in patients undergoing long-term hemodialysis, a deficiency in serum free carnitine can disrupt myocardial fatty acid metabolism, and the administration of exogenous *L*-carnitine can restore normalcy in this situation. These findings support a role of carnitine deficiency in the development of cardiac dysfunction associated with chronic uremia.

References

1 Lazarus JM, Lowrie EG, Hampers CL, Merrill JP: Cardiovascular disease in uremic patients on hemodialysis. Kidney Int 1975;7(suppl): 167–175.
2 Coratelli P, Bougiorno E, Petrarulo F, Corciulo R, Giannattasio M, Passavanti G, Antonelli G: Pathogenic aspects of uremic cardiomyopathy. Miner Electrolyte Metab 1989;15:246–253.
3 Frits IB: Carnitine and its role in fatty acid metabolism. Adv Lipid Res 1963;1:285–334.
4 Opie LH: Role of carnitine in fatty acid metabolism of normal and ischemic myocardium. Am Heart J 1979;97:375–388.
5 Zales VR, Benson DW Jr: Reversible cardiomyopathy due to carnitine deficiency from renal tubular wasting. Pediatr Cardiol 1995;16: 76–78.
6 Suzuki Y, Narita M, Yamazaki N: Effects of *L*-carnitine on arrhythmias during hemodialysis. Jpn Heart J 1982;23:349–359.
7 Khoss AE, Steger H, Legenstein E, Proll E, Salzer-Muhar U, Schlemmer M, Balzar E, Wimmer M: *L*-Carnitintherapie und Myokardfunktion bei chronisch hämodialysierten Kindern. Wien Klin Wochenschr 1989;101:17–20.
8 Kudoh Y, Shoji T, Oimatsu H, Yoshida S, Kikuchi K, Iimura O: The role of *L*-carnitine in the pathogenesis of cardiomegaly in patients with chronic hemodialysis. Jpn Circ J 1983;47: 1391–1397.
9 Golper TA, Ahmad S: *L*-Carnitine administration to hemodialysis patients: Has its time come? Semin Dial 1992;5:94–98.
10 Savica V, Bellinghieri G, Stefano CD, Corvaja E, Consolo F, Corsi M, Maccari F, Spagnoli LG, Villaschi S, Palmieri G: Plasma and muscle carnitine levels in hemodialysis patients with morphological-ultrastructural examination of muscle samples. Nephron 1983;35:232–236.
11 Knapp FF Jr, Kropp J, Goodman MM, Franken P, Reske SN, Ambrose KR, Som P, Biersack HJ, Sloof GW, Visser FC: The development of iodine-123-methyl-branched fatty acids and their applications in nuclear cardiology. Ann Nucl Med 1993;7(suppl 2):1–14.
12 Takahashi M, Ueda S, Misaki H, Sugiyama N, Matsumoto K, Matsuo N, Murao S: Carnitine determination by an enzymatic cycling method with carnitine dehydrogenase. Clin Chem 1994;40:817–821.
13 Fujibayashi Y, Yonekura Y, Tamaki K, Yamamoto K, Som P, Knapp FF Jr, Konishi J, Yokoyama A: Myocardial accumulation of BMIPP in relation to ATP concentration. Ann Nucl Med 1993;7(suppl 2):15–18.
14 Kropp J, Likungu J, Kirchhoff PG, Knapp FF Jr, Reichmann K, Reske SN, Biersack HJ: Single photon emission tomography imaging of myocardial oxidative metabolism with 15-(*p*-[123]-I)iodophenyl) pentadecanoic acid in patients with coronary artery disease and aortocoronary bypass graft surgery. Eur J Nucl Med 1991;18:467–474.
15 Bellinghieri G, Savica V, Mallamace A, Stefano CD, Consolo F, Spagnoli LG, Villaschi S, Palmieri G, Corsi M, Maccari F: Correlation between increased serum and tissue *L*-carnitine levels and improved muscle symptoms in hemodialyzed patients. Am J Clin Nutr 1983;38: 523–531.
16 Fagher B, Cederblad G, Monti M, Olsson L, Rasmussen B, Thysell H: Carnitine and left ventricular function in haemodialysis patients. Scand J Clin Lab Invest 1985;45:193–198.
17 Opie LH: Chronic stunning: The new switch in thought. Invited Comment. Basic Res Cardiol 1995;90:303–304.