Long-Term Levocarnitine Ameliorates Left Ventricular Diastolic as Well as Systolic Dysfunction in Hemodialysis Patients — Multi-Center Study —

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Background: Levocarnitine has been reported to improve the left ventricular (LV) systolic function and decrease LV hypertrophy in hemodialysis (HD) patients. Its effect on LV diastolic dysfunction, however, has not yet been clarified.

Methods and Results: HD patients (n=88) were given levocarnitine i.v. 1,000 mg for 12 months at the end of every dialysis session through the dialysis circuit of the venous site. LV ejection fraction (EF), E/A, E/e’, left atrial volume index (LAVI) and LV mass index (LVMI) were measured before and 3, 6, 9, and 12 months after the start of levocarnitine on echocardiography. We regarded E/A≤0.8, E/e’>14 and LAVI>34 mL/m² as LV diastolic dysfunction, and LVEF<55% as LV systolic dysfunction. We also investigated the effect of levocarnitine on HFpEF. Plasma brain natriuretic peptide, total carnitine, free carnitine, and acyl-carnitine and biochemistry parameters were measured. Levocarnitine significantly improved LV diastolic function in HD patients with LV diastolic dysfunction, but did not affect LV diastolic function in those with normal LV diastolic function. Levocarnitine significantly improved HFpEF. Levocarnitine significantly improved the LV systolic function in HD patients with LV systolic dysfunction but did not affect the LV systolic function in those with normal LV systolic function. Levocarnitine significantly decreased LVMI and increased plasma total, free, and acyl-carnitine.

Conclusions: Levocarnitine ameliorates LV diastolic as well as LV systolic dysfunction in HD patients.

Key Words: Hemodialysis; HFpEF; Levocarnitine; LV diastolic dysfunction; LV systolic dysfunction
of patients was small. A recent randomized controlled study with a large number of HD patients and 12-month treatment with levocarnitine demonstrated that levocarnitine improved the LV ejection fraction (LVEF; LV systolic function) and decreased LVH. The long-term effect of levocarnitine on LV diastolic dysfunction in HD patients, however, has not yet been fully elucidated. Hence, in the present study, we investigated the effects of long-term levocarnitine, focusing on LV diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) in HD patients.

Methods

Ninety-six patients who were undergoing HD at 8 hospitals: Asahi University Hospital, Chuno Kosei Hospital, Hashima Municipal Hospital, Sawada Hospital, Yamauchi Hospital, Gihoku Kosei Hospital, Hirano Hospital, and Gifu Prefectural Gero Hospital, were included in this study. The patients were enrolled consecutively according to the following inclusion criteria: (1) HD>6 months; and (2) no history of carnitine use. The exclusion criteria were: (1) hypersensitivity to levocarnitine; (2) pregnancy; or (3) inclusion judged as inappropriate by the attending physician.

Of the 96 HD patients enrolled, 88 patients could be followed up for 12 months after the start of this study. Eight patients were excluded from the data analysis (3 died of complications and 5 patients did not have data available at 12 months). Of the 88 patients, 61 were male and 27 were female. Mean patient age was 65.1±11.4 years old, and the mean duration of HD was 4.5±5.7 years.

The protocol was approved by the Ethics Committee of Gifu University Graduate School of Medicine (approval number: 26-83). All patients provided written informed consent before the study commenced. The investigation conformed to the principles outlined in the Declaration of Helsinki. The public and trial registry number was R000040056.

Protocol

The HD patients were given 1,000 mg i.v. levocarnitine at the end of HD through a dialysis circuit in the venous site at the end of every HD session and followed up for 12 months.

LV Diastolic and Systolic Function

Echocardiography was performed at 24 h after HD to measure LV diastolic and systolic function. With regard to LV diastolic function, E/A≤0.8, E/e’>14 (average of septal and lateral site measurement) or left atrial volume index (LAVI)>34 mL/m² was defined as LV diastolic dysfunction according to the guidelines of the American Society of Echocardiography and European Association of Cardiovascular Imaging. E/A, E/e’ and LAVI were measured before and 3, 6, 9, and 12 months after the start of levocarnitine. To measure LV systolic function, LVEF was measured before and 3, 6, 9, and 12 months after the start of levocarnitine. LVEF<55% was defined as LV systolic dysfunction. LVF could be followed up in 88 patients. E/A could be followed up in 87 patients because 1 patient with atrial fibrillation (AF) was excluded. E/e’ could be followed up in 86 patients because E/e’ was not measured in one patient. LAVI could be followed up in 85 patients because 2 patients who could not obtain the data at 12 months were excluded.

Effect of Levocarnitine on HFpEF

The effect of levocarnitine on HFpEF was investigated. HFpEF was defined as LVEF>50% and LAVI>34 mL/m², LVEF>50% and E/e’>14, and LVEF>50% and e’<7 cm/s (measured at septal site) according to the guidelines for diagnosis and treatment of acute and chronic heart failure (JCS 2017/JHFS 2017).

LVM

Echocardiography was performed to measure LVM before and 3, 6, 9, and 12 months after the start of levocarnitine. LVM (g) =0.8×[(LVDd+IVSth+PWth)−(LVDd)]+0.6, where LVDd is LV end-diastolic dimension, IVSth is interventricular septum thickness, and PWth is posterior wall thickness. Body height and weight were measured to calculate the body surface area; LVM was indexed per square area (LVMI g/m²).

Plasma Carnitine

Blood samples were taken from the antecubital veins at 24 h after HD. Plasma carnitine (total carnitine, free carnitine, and acyl-carnitine) were measured using LC/MS/MS before and, 3, 6, and 12 months after the start of levocarnitine treatment.

Brain Natriuretic Peptide (BNP)

Changes in BNP, an indicator of heart failure, were measured at 24 h after HD before and 3, 6, 9, and 12 months after the start of levocarnitine.

Blood Biochemistry

Blood samples were taken from the antecubital veins at 24 h after HD. Hemoglobin (Hb), hematocrit (Ht), calcium (Ca), phosphorus (P), intact parathyroid hormone (iPTH), total bilirubin (T-Bil), aspartate transaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), blood urea nitrogen (BUN), creatinine (Cr), and BNP were measured before and 3, 6, 9, and 12 months after the start of levocarnitine.

Statistical Analysis

Data are given as mean±SD. The normality of data distributions was tested using the Kolmogorov-Smirnov test. This was a prospective cohort study. Given that we divided the data into 2 groups: LV normal diastolic function and LV diastolic dysfunction, or LV normal systolic function and LV systolic dysfunction, respectively, there was a concurrent control in this study.

To assess the effect of 12-month treatment of levocarnitine on cardiac function and LVM, we could not use one-way ANOVA with repeated measures, because the data at 3, 6, and 9 months were sometimes defective. Therefore, the effect of levocarnitine treatment for 12 months was assessed using the perfect paired data before and at 12 months with the paired Student’s t-test. In addition, the difference between before and at 12 months was compared between patients with normal LV function and LV dysfunction using the unpaired Student’s t-test. Assessment of unpaired data between groups before and at 3, 6, 9, and 12 months was performed using 1-way ANOVA followed by multiple comparison with Tukey method. This statistical analysis was performed using GraphPad Prism 7 (GraphPad Software). Univariate analysis was performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R.
Results

Diastolic Function According to E/A, E/e' and LAVI

We divided HD patients into 2 groups before levocarnitine treatment according to E/A: E/A≤0.8 and E/A>0.8 (Figure 1A). In the E/A>0.8 group, E/A was 1.08±0.25 (n=49), 1.03±0.21 (n=46), 1.02±0.16 (n=45), 1.03±0.17 (n=44), and 1.04±0.23 (n=49) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively. In the E/A≤0.8 group, it was 0.71±0.09 (n=38), 0.74±0.14 (n=38), 0.82±0.19 (n=31), 0.80±0.14 (n=31), and 0.76±0.17 (n=38) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively. In the E/A≤0.8 (LV diastolic dysfunction) group, E/A was significantly increased at 6 months as compared with that before treatment (Figure 1A). Levocarnitine significantly increased E/A at 12 months as compared with before levocarnitine treatment when paired data were assessed (Figure 1B), but in patients with E/A>0.8 (LV normal diastolic function), levocarnitine did not affect E/A (Figure 1A,B).

The HD patients were then divided into 2 groups according to E/e': E/e'>14 and E/e'≤14 (Figure 1C). In the E/e'>14 group, E/e' was 18.8±4.4 (n=24), 13.7±3.9 (n=23), 14.4±6.7 (n=17), 14.9±5.8 (n=19), and 16.2±5.5 (n=24) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively. In the E/e'≤14 group, it was 11.0±2.0 (n=62), 10.6±2.1 (n=62), 11.2±2.5 (n=60), 10.0±2.0 (n=56), and 10.7±2.3 (n=62) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively. In the E/e'>14 (LV diastolic dysfunction) group, E/e' significantly decreased at 3 months as compared with that before treatment (Figure 1C). Levocarnitine significantly decreased E/e' at 12 months as compared with that before levocarnitine treatment when paired data were assessed (Figure 1D), but in patients with E/e'≤14 (LV normal diastolic function), levocarnitine did not affect E/e' (Figure 1C,D).

The HD patients were then divided into 2 groups according to LAVI: LAVI>34 mL/m² and LAVI≤34 mL/m² (Figure 2A). In the LAVI>34 mL/m² group, LAVI was 43.7±10.2 (n=41), 38.6±11.0 (n=40), 37.1±12.8 (n=37), 31.2±8.7 (n=31), and 35.2±13.3 mL/m² (n=41) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively. In the LAVI≤34 mL/m² group, it was 25.4±4.4 (n=44), 25.9±7.3 (n=40), 25.5±7.7 (n=40), 25.2±7.4 (n=43), and 24.3±7.3 mL/m² (n=44) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively. In patients with LAVI>34 mL/m² (LV diastolic dysfunction), LAVI significantly decreased at 3, 6, 9 and 12 months as compared with before treatment (Figure 2A). Levocarnitine significantly decreased LAVI at 12 months as compared with that before levocarnitine treatment when paired data were assessed (Figure 2B). In the LAVI≤34 mL/m² (LV normal diastolic function) group, however, levocarnitine did not affect LAVI (Figure 2A,B).

LV Systolic Function According to LVEF

We divided patients into 2 groups: LVEF≥55% and
Levocarnitine Ameliorates LV Diastolic Dysfunction

Levocarnitine treatment significantly increased LVEF at 12 months as compared with before, when paired data were assessed (Figure 2D). In patients with LVEF≥55% (LV normal systolic function), however, levocarnitine did not affect LVEF (Figure 2C).

**Effect of Levocarnitine on HFpEF**

Levocarnitine treatment significantly improved the deteriorated E/e', LAVI and e' at 12 months as compared with before treatment (Figure 2C).
**Figure 4.** (A,C) Change in (A) left ventricular mass index (LVMI) and (C) brain natriuretic peptide (BNP) over 12 months of levocarnitine treatment in hemodialysis patients; and (B,D) comparison of before vs. after 12 months of treatment for (B) LVMI and (D) BNP. *P<0.05, **P<0.01, ***P<0.001. M, months.

**Figure 5.** Change in (A) total carnitine, (B) free carnitine and (C) acyl-carnitine over 12 months of levocarnitine treatment in hemodialysis patients. (D) Change in biochemistry data over 12 months of levocarnitine treatment in hemodialysis patients. ALT, alanine aminotransferase; AST, aspartate transaminase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Ca, calcium; CK, creatine kinase; Cr, creatinine; Hb, hemoglobin; Ht, hematocrit; iPTH, intact parathyroid hormone; LDH, lactate dehydrogenase; P, phosphorus; T-Bil, total bilirubin. ***P<0.001. M, months.
Levocarnitine Ameliorates LV Diastolic Dysfunction

Plasma Carnitine

Plasma total carnitine was 73.9±66.1 (n=76), 276.0±132.7 (n=87), 290.8±143.8 (n=79), 303.3±163.8 (n=79), and 293.3±141.3 ng/mL (n=87) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively (Figure 5A). Plasma total carnitine significantly increased at 3, 6, 9, and 12 months after the start of levocarnitine treatment as compared with that before treatment.

Plasma free carnitine was 33.8±24.9 (n=53), 222.0±56.1 (n=54), 242.1±68.9 (n=46), 270.3±73.3 (n=44), and 253.0±62.0 ng/mL (n=54) before and 6, 9, and 12 months after the start of levocarnitine, respectively (Figure 5B). Plasma free carnitine significantly increased at 3, 6, 9, and 12 months after the start of levocarnitine as compared with that before treatment.

Plasma acyl-carnitine was 20.0±17.3 (n=54), 129.7±44.4 (n=54), 146.2±45.5 (n=46), 166.2±62.5 (n=44), and 152.9±49.2 ng/mL (n=54) before and 3, 6, 9, and 12 months after the start of levocarnitine treatment, respectively, and significantly increased at 3, 6, 9 and 12 months after the start of levocarnitine as compared with that before treatment (Figure 5C).

Effect on LVMI

LVMI was 143.1±34.3 (n=88), 135.5±35.2 (n=87), 130.0±31.4 (n=78), 128.3±25.2 (n=79), and 131.9±31.6 g/m² (n=88) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively (Figure 4A). LVMI significantly decreased at 6, 9, and 12 months as compared with before levocarnitine treatment. Levocarnitine treatment significantly decreased LVMI at 12 months as compared with that before levocarnitine treatment, when paired data were assessed (Figure 4B).

Effect on BNP

BNP was 327.4±377.8 (n=88), 264.4±158.1 (n=81), 214.2±158.1 (n=71), and 273.1±393.3 pg/mL (n=88) before and 3, 6, 9, and 12 months after the start of levocarnitine, respectively. BNP significantly decreased at 9 months as compared with before treatment (Figure 4C). Levocarnitine treatment did not affect LVMI at 12 months as compared with that before treatment, when paired data were assessed (Figure 4D).

Data given as mean±SD or n (%). A, atrial systolic wave; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; CCB, calcium channel blockers; DM, diabetes mellitus; E, early diastolic wave; e’, early diastolic wall motion velocity; HD, hemodialysis; HL, hyperlipidemia; HTN, hypertension; LVMI, left ventricular mass index.

| Characteristics | E/A>0.8 (n=49) | E/A<0.8 (n=38) | P-value |
|-----------------|---------------|----------------|---------|
| Age (years)     | 63.3±9.6      | 67.4±13.1      | 0.084   |
| Sex (M/F)       | 33 (67) / 16 (33) | 27 (71) / 11 (29) | 0.715   |
| DM              | 26 (53)       | 17 (45)        | 0.447   |
| HTN             | 41 (84)       | 68 (48)        | 0.095   |
| HL              | 10 (20)       | 9 (24)         | 0.718   |
| LVMI decrease   | 39 (80)       | 23 (61)        | 0.052   |

| Characteristics | E/e’>14 (n=24) | E/e’≤14 (n=62) | P-value |
|-----------------|---------------|---------------|---------|
| Age (years)     | 65.0±12.6     | 65.1±11.1     | 0.947   |
| Sex M/F         | 17 (71) / 7 (29) | 43 (69) / 19 (31) | 0.895   |
| DM              | 13 (54)       | 28 (45)       | 0.459   |
| HTN             | 15 (63)       | 51 (82)       | 0.052   |
| HL              | 6 (25)        | 14 (23)       | 0.814   |
| LVMI decrease   | 19 (79)       | 43 (69)       | 0.369   |
Carnitine is a natural compound mainly derived from dietary sources such as red meat, fish, and dairy products. In humans, most carnitine is absorbed from the small intestine, although a small amount is synthesized in the liver, kidney, and brain from the amino acids lysine and methionine. Most total body carnitine is found in skeletal muscle, and a small amount is found in the liver and kidney. The myocardium and skeletal muscle totally depend on carnitine uptake from the blood. Carnitine is present in free and esterified forms. In the myocardium, carnitine plays a crucial role in energy metabolism of both fatty acids and carbohydrates, and in transporting activated long chain fatty acids (acyl-CoAs) from the cytosol into the mitochondrial matrix where β-oxidation and the subsequent production of ATP occur.

Carnitine deficiency in HD patients is caused by the loss of carnitine during HD, and contributes to the pathogenesis of cardiomegaly in HD patients. As noted, carnitine is involved in myocardial fatty acid metabolism by transporting long-chain fatty acids from the cytoplasm to before treatment (Figure 5C).

**Blood Biochemistry**

The levels of Hb, Ht, Ca, P, PTH, T-Bil, AST, ALT, LDH, CK, BUN and Cr before and 3, 6, 9, and 12 months after levocarnitine treatment are listed in Figure 5D. There was no significant change in any parameter during the 12 months.

**Factors That May Affect LV Diastolic and Systolic Function**

On univariate analysis, some factors that may be associated with LV diastolic function were compared according to E/A≤0.8 and E/A>0.8, and according to E/e’>14 and E/e’≤14 groups (Table 1), and between LAVI>34 and LAVI≤34 mL/m² (Table 2). There was no difference in these factors between E/A≤0.8 and E/A>0.8, or between E/e’>14 and E/e’≤14. There was also no difference in these factors between LAVI>34 and LAVI≤34 mL/m², except for hypertension, which was more frequent in the LAVI≤34 mL/m² group, which might not have contributed to the improvement of LAVI in the LAVI>34 mL/m² group (Table 2). There was no difference in these factors between the LVEF≥55% and LVEF<55% groups (Table 2).

**Discussion**

Carnitine is a natural compound mainly derived from dietary sources such as red meat, fish, and dairy products. In humans, most carnitine is absorbed from the small intestine, although a small amount is synthesized in the liver, kidney, and brain from the amino acids lysine and methionine. Most total body carnitine is found in skeletal muscle, and a small amount is found in the liver and kidney. The myocardium and skeletal muscle totally depend on carnitine uptake from the blood. Carnitine is present in free and esterified forms. In the myocardium, carnitine plays a crucial role in energy metabolism of both fatty acids and carbohydrates, and in transporting activated long chain fatty acids (acyl-CoAs) from the cytosol into the mitochondrial matrix where β-oxidation and the subsequent production of ATP occur.

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Levocarnitine Ameliorates LV Diastolic Dysfunction

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Author Contributions
Shinya M. & H. Ohashi designed the experiment, J.N., H. Ohashi, M.O., M.S., K.H., A.K., N.T., T.K., H.T.O., K.N., K.G., I.M., and G.Y. collected data. Shingo M. performed statistical analysis. H. Okura performed data interpretation, and J.N. and Shinya M. wrote the manuscript.

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Disclosures
Shinya M. is a member of Circulation Reports’ Editorial Team. The other authors declare no conflicts of interest.

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