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Effects of switching from oral administration to intravenous injection of L-carnitine on lipid metabolism in hemodialysis patients

Kei Fukami[1], Sho-ichi Yamagishi[2], Kazuko Sakai[1], Makoto Nasu[1] and Seiya Okuda[1]

[1]Division of Nephrology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan and [2]Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Japan

Correspondence and offprint requests to: Kei Fukami; E-mail: fukami@med.kurume-u.ac.jp

Abstract

Background. Carnitine deficiency may contribute to cardiovascular disease (CVD) in patients with hemodialysis (HD). Dyslipidemia plays a role in CVD and its prevalence is also high in HD patients. We examined here the effects of switching from oral administration (PO) to intravenous (IV) injection of L-carnitine on lipid metabolism in patients with HD.

Methods. Nine HD patients who had received L-carnitine orally (900 mg/day) for 1 year were enrolled in this study. We examined whether lipid parameters were improved by switching to IV injection therapy of 1000 mg L-carnitine.

Results. IV injection of L-carnitine for 1 week significantly increased total, free and acyl carnitine levels both before and after HD. Switching to IV injection therapy for 1 and 4 weeks decreased serum free fatty acid (FFA) (322 ± 104 versus 261 ± 124 μmol/L) and increased high-density lipoprotein-cholesterol levels (1.46 ± 0.49 versus 1.63 ± 0.62 mmol/L), respectively. Change in FFA values from the baseline (ΔFFA) was positively correlated with the Δacyl/free carnitine ratio ($r^2 = 0.553$, $P = 0.022$).

Conclusion. This study demonstrated that switching to IV L-carnitine therapy from oral supplementation improved lipid profiles, thus supporting the clinical utility of IV administration of L-carnitine for the treatment of patients on HD.

Keywords: free fatty acid; HDL-cholesterol; hemodialysis; L-carnitine

Introduction

Carnitine is a natural substance, which is not only supplied through the intake of protein-rich foods, but also synthesized by the liver, kidney and brain, and excreted from the kidney in humans [1]. Because about 80% of serum carnitine is eliminated from the blood via hemodialysis (HD) [1, 2], carnitine deficiency is often observed in patients with HD.

Carnitine participates in fatty acid β-oxidation and energy production by transporting long-chain fatty acids from the cytoplasm to mitochondria, in particular, in muscles [3]. Carnitine also regulates the function of mitochondrial respiratory chain, energy production and elimination of excess intracellular fatty acids. Therefore, carnitine deficiency may cause muscle weakness and cardiac hypertrophy in humans [4, 5]. In addition, L-carnitine supplementation has been reported to inhibit arrhythmias, increase cardiac output and exercise capacity and improve muscle symptoms in HD patients [6]. Moreover, we have recently found that carnitine deficiency is associated with decreased testosterone and increased pentosidine levels in patients with HD [7], thus suggesting that HD-related loss of carnitine might be involved in accelerated atherosclerosis and the high prevalence of cardiovascular disease (CVD) in these subjects.

Dyslipidemia is one of the strongest risk factors for CVD in patients with HD, an abnormality of which is frequently observed in HD patients [8, 9]. However, the relationship between carnitine deficiency and dyslipidemia remains unknown in patients with HD. Further, it is unclear whether L-carnitine supplementation could improve the lipid abnormalities in these patients, and if so, whether the difference in the route of administration of L-carnitine may have different effects on lipid parameters. Therefore, in this study, we compared the effects of oral and intravenous (IV) administration of L-carnitine on dyslipidemia in HD patients. For this, we investigated whether the lipid parameters were improved by switching from oral administration (PO) to IV injection of L-carnitine therapy in patients with HD.

Materials and methods

Subjects and protocol

Nine maintenance HD patients (five male and four female; mean age, 69.1 ± 13.5 years; mean duration of

HD, 88.9 ± 71.6 months; three chronic glomerulonephritis, one diabetic nephropathy, one glomerulosclerosis and four unknown etiology) who had received PO of L-carnitine P.O. (900 mg/day) for 1 year were enrolled in this study. Patients were dialyzed for 4–5 h with high-flux dialyzers three times a week. Nine age- and sex-matched subjects (four male and five female; mean age, 63.4 ± 5.6 years) were used as control. The HD patients underwent a complete history, physical examinations and determinations of blood chemistries including total, free and acyl carnitine and serum free fatty acid (FFA) levels just before and after HD. Then, the route of L-carnitine supplementation was changed from PO to IV. After switching to IV L-carnitine administration (1000 mg after every HD session) for a week, blood was drawn just before and after HD to determine total, free and acyl carnitine and FFA levels again. These biochemical variables were measured with the enzymatic method as described previously (SRL, Inc., Tokyo, Japan) [10]. Further, before and 1 month after the IV replacement therapy, hemoglobin, albumin, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), alkaline phosphatase, blood urea nitrogen, creatinine, uric acid, calcium, phosphate and C-reactive protein (CRP) levels were also measured just before the HD session at a commercially available laboratory as described previously (Wako Pure Chemical Industries Ltd, Osaka, Japan) [11]. Low-density lipoprotein (LDL) cholesterol levels were calculated by the Friedewald formula [12].

Informed consent was obtained from all subjects, and the study protocol was approved by the Institutional Ethics Committees of Kurume University School of Medicine and Sugi Cardiovascular Hospital, Japan. This work was conducted in accordance with the Declaration of Helsinki. This trial was registered with the University Hospital Medical Information Network clinical trials database (UMIN000010953).

Statistical analysis

Data are shown as mean ± SD. Clinical variables, which were not normally distributed such as TG and CRP, were log-transformed. Analyses of significant differences of variables between before and after HD and between before and after switching to IV L-carnitine treatment were performed using a paired *t*-test. Significant differences of carnitine levels between HD patients and age- and sex-matched control subjects were examined using the unpaired *t*-test. Correlations between changes in FFA levels from the baseline (ΔFFA) after IV therapy and Δacyl/free carnitine ratio were determined by a linear regression analysis. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with SPSS system ver.20 (Chicago, IL, USA).

Results

Serum carnitine levels before and after switching to IV therapy

Total and free carnitine levels before L-carnitine supplementation just before HD session were significantly lower in HD patients compared with those in age- and sex-matched healthy controls ($n = 9$) [total carnitine; 38.1 ± 4.4 versus 56.9 ± 6.3 μmol/L ($P < 0.001$), free carnitine; 23.5 ± 2.7 versus 44.9 ± 5.5 μmol/L ($P < 0.001$)]. Serum carnitine levels before HD were significantly higher in patients who received PO therapy for 1 year than those in age- and sex-matched healthy controls (total carnitine; 230.6 ± 69.1 versus 56.9 ± 6.3 μmol/L ($P < 0.001$), free carnitine; 146.7 ± 50.1 versus 44.9 ± 5.5 μmol/L ($P < 0.001$) and acyl carnitine; 83.9 ± 21.4 versus 12.0 ± 3.1 μmol/L ($P < 0.001$), respectively). Levels of all the carnitine fractions were significantly decreased after the HD session ($P < 0.001$). Total, free and acyl carnitine levels before HD were significantly increased by switching to IV therapy for 1 week [total carnitine; 324.6 ± 83.1 versus 230.6 ± 69.1 μmol/L ($P < 0.01$), free carnitine; 203.8 ± 49.9 versus 146.7 ± 50.1 μmol/L ($P < 0.001$) and acyl carnitine; 120.8 ± 37.2 versus 83.9 ± 21.4 μmol/L ($P < 0.05$)]. Although these values were decreased after

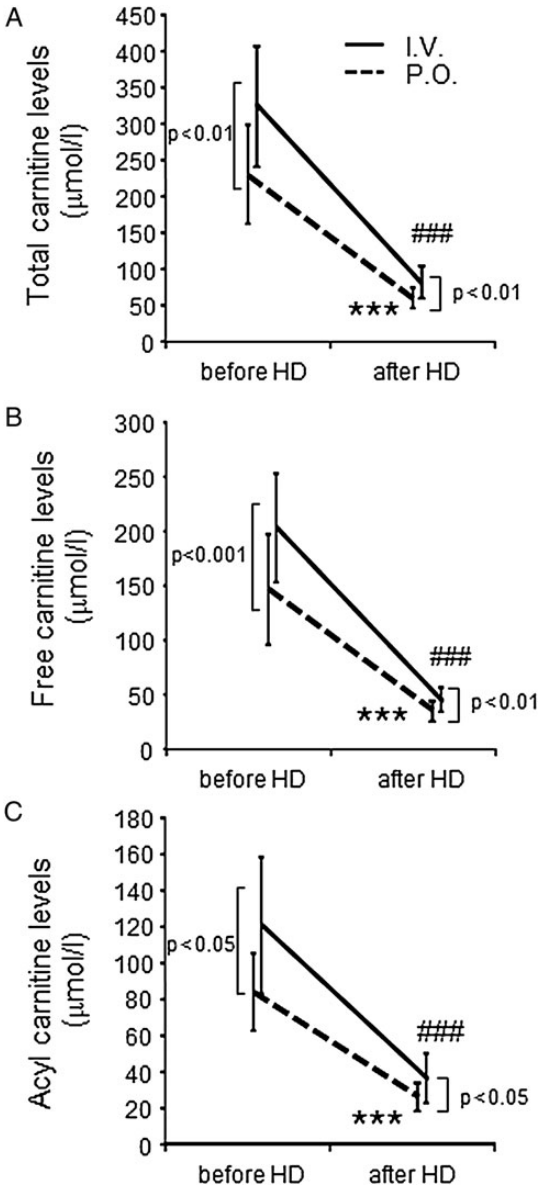

Fig. 1. Serum carnitine levels before and after HD in patients treated with PO or IV supplementation therapy of L-carnitine. (**A**) Total carnitine, (**B**) free carnitine and (**C**) acyl carnitine levels. A solid line; IV of L-carnitine, a dotted line; PO of L-carnitine. ***$P < 0.001$ versus before HD in patients treated with PO of L-carnitine. ###$P < 0.001$ versus before HD in patients treated with IV of L-carnitine. $n = 9$. HD, hemodialysis; IV, intravenous injection; PO, oral administration.

the HD session, the levels were still significantly higher than those of patients who received PO therapy for 1 year [total carnitine; 81.5 ± 21.6 versus 61.2 ± 13.9 μmol/L ($P < 0.001$), free carnitine; 45.2 ± 11.2 versus 35.1 ± 8.7 μmol/L ($P < 0.001$) and acyl carnitine; 36.3 ± 13.6 versus 26.1 ± 7.8 μmol/L ($P < 0.01$)] (Figure 1).

Effects of switching to IV L-carnitine injection on lipid parameters

We next examined whether switching from PO to IV of L-carnitine treatment could affect clinical variables including lipid profiles in HD patients. Serum FFA levels were significantly reduced by L-carnitine IV replacement therapy for 1 week (322 ± 104 versus 261 ± 124 μmol/L, $P < 0.05$, Figure 2A). ΔFFA values were positively and independently associated with Δacyl/free carnitine ratio ($r^2 = 0.553$, $P = 0.022$, Figure 2B). Further, as shown in Table 1, switching to IV therapy for 1 month significantly increased HDL-cholesterol levels (1.46 ± 0.49 versus 1.63 ± 0.62 mmol/L, $P = 0.048$) and had a tendency to decrease the LDL–HDL ratio (1.69 ± 0.75 versus 1.58 ± 0.78, $P = 0.077$) in HD patients.

Discussion

We demonstrated here that switching from PO to IV administration of L-carnitine therapy significantly increased serum levels of all the carnitine fractions (total, free and acyl carnitine levels) in HD patients. Furthermore, switching to IV therapy also significantly increased HDL-cholesterol and decreased FFA levels in HD subjects, and ΔFFA values were positively correlated with the Δacyl/free carnitine ratio.

Low HDL-cholesterol levels are one of the strongest risk factors that could predict future cardiovascular events in high-risk patients, including HD subjects [9, 13, 14]. Indeed, HDL-cholesterol levels were inversely associated with high-sensitive CRP values, one of the independent factors predicting mortality in patients with HD [15, 16]. Furthermore, Barter *et al.* [9] have demonstrated that HDL-cholesterol levels are predictive of major cardiovascular events in statin-treated high-risk patients for CVD with low LDL-cholesterol levels. These observations suggest that low HDL-cholesterol might be a residual risk for CVD and a novel therapeutic target even in HD patients whose LDL-cholesterol values were well-controlled [17]. We have

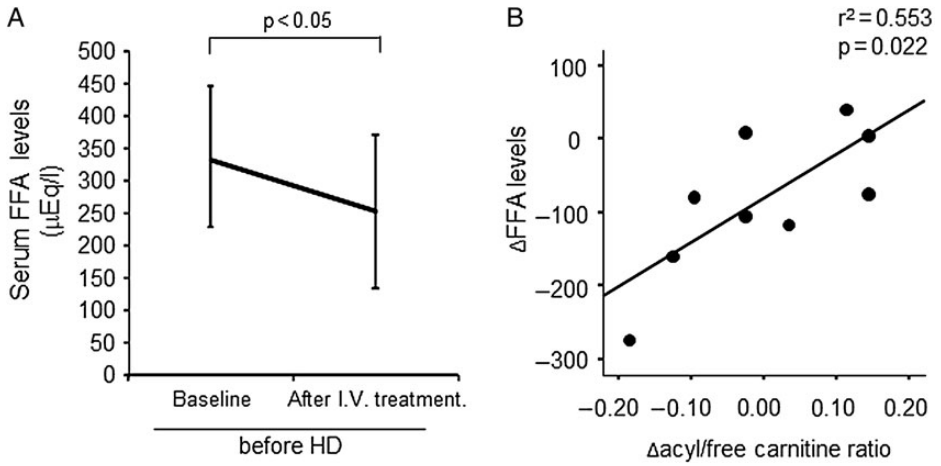

Fig. 2. (**A**) Effect of switching to IV of L-carnitine on serum FFA levels before HD. (**B**) Correlation between change in FFA values from the baseline (ΔFFA) and Δacyl/free carnitine ratio $n = 9$. FFA, free fatty acid; HD, hemodialysis; IV, intravenous injection; PO, oral administration; Δ, delta.

Table 1. Clinical variables before and after switching from oral to IV L-carnitine supplementation

	Before switching	After switching	P-value
Hemoglobin g/L	111 ± 10	113 ± 10	0.629
Serum albumin g/L	36.4 ± 2.8	36.6 ± 2.4	0.842
ALP U/L	260 ± 122	274 ± 144	0.338
LDLc mmol/L (mg/dL)	2.23 ± 0.68 (86.4 ± 26.4)	2.28 ± 0.71 (88.2 ± 27.4)	0.488
HDLc mmol/L (mg/dL)	1.46 ± 0.49 (56.3 ± 18.8)	1.63 ± 0.62 (63.0 ± 23.9)	0.048
LDLc/HDLc ratio	1.69 ± 0.75	1.58 ± 0.78	0.077
TG[a] mmol/L [range] (mg/dL)	1.1 [0.5–16] (95 [46–137])	1.2 [0.2–2.6] (108 [17–227])	0.933
BUN mmol/L (mg/dL)	21.7 ± 4.8 (60.9 ± 13.1)	24.4 ± 4.2 (68.4 ± 11.8)	0.056
Serum Cr mmol/L (mg/dL)	886 ± 209 (10.0 ± 2.4)	903 ± 209 (10.2 ± 2.4)	0.292
cCa mmol/L (mg/dL)	2.27 ± 0.08 (9.10 ± 0.34)	2.30 ± 0.09 (9.22 ± 0.35)	0.223
P mmol/L (mg/dL)	1.52 ± 0.29 (4.71 ± 0.90)	1.76 ± 0.42 (5.46 ± 1.30)	0.098
CRP[a] μg/L (range)	2400 (200–9400)	1400 (400–4000)	0.232

Values are shown as mean ± SD or range.
ALP, alkaline phosphatase; LDLc, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol; TG, triglycerides; BUN, blood urea nitrogen; Cr, creatinine; cCa, corrected calcium; P, phosphate; CRP, C-reactive protein.
[a]These variables are shown in the original scale after using log-transformed values.

previously found that oral L-carnitine supplementation significantly increases LDL-cholesterol and TG levels, but it did not affect HDL-cholesterol values in patients with HD [18]. In this study, switching to IV injection therapy with L-carnitine significantly increased HDL-cholesterol levels and had a tendency to decrease the LDL–HDL ratio. These results suggest that IV therapy of L-carnitine might be superior to PO treatment in restoring the carnitine levels and increasing the HDL-cholesterol values, which could lead to the risk reduction of future cardiovascular events in patients with HD.

Circulating levels of FFA were higher in uremic patients, which were associated with high-sensitivity CRP values and carotid atherosclerosis [19–22]. These observations suggest that circulating FFA levels might also be a marker of CVD and death in patients with HD [19, 20]. In this study, switching from PO to IV administration of L-carnitine significantly reduced serum FFA values in HD patients. Although we did not know the exact mechanism by which IV L-carnitine therapy decreased the FFA values in our subjects, carnitine is known to be indispensable in transporting FFA into the mitochondrial matrix for β-oxidation. Therefore, increased carnitine levels by IV supplementation therapy could improve the clearance of circulating FFA and resultantly reducing the values in HD patients. Another possibility is that the decreased ratio of acyl/free carnitine by IV carnitine supplementation therapy might be involved in the reduction of FFA levels, because the Δacyl/free carnitine ratio was positively and independently associated with ΔFFA values in our subjects. The acyl/free carnitine ratio is increased in patients with HD [2], and long-term carnitine supplementation has been shown to reduce the acyl/free carnitine ratio in these patients [23]. Because free carnitine could remove an excess of acyl CoA intermediates from mitochondria as acyl carnitine as well [24], the increased acyl/free carnitine ratio could impair the metabolism of FFA, thus leading to the elevation of FFA values in patients with HD. Furthermore, acyl carnitine is reported to induce oxidative stress generation and cause insulin resistance in HD subjects [24]. In addition, administration of L-carnitine has been shown to inhibit protein glycation and oxidative stress generation in precataractous lens from fructose-fed rats [25]. Therefore, impaired balance of total, free and acyl carnitine levels might partly explain the increased risk for CVD in patients with HD.

Conclusion

This study demonstrated that switching to IV from PO administration of L-carnitine therapy improved lipid profiles, thus supporting the clinical utility of IV L-carnitine supplementation in HD patients. However, our sample size was small, the observational period short and there was no untreated control group. Therefore, we cannot totally exclude the risk of a type 1 error. Further longitudinal and multicenter studies with large sample size are needed to clarify whether switching to IV administration of L-carnitine could improve lipid abnormalities and resultantly decrease future CVD events in HD subjects.

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Conflict of interest statement. Dr Fukami has received honoraria such as lecture fees from Otsuka (Otsuka Pharmaceutical Co., Ltd.). This paper has not been published previously in whole or part, except in abstract format.

(See related article by Sanchez-Niño and Ortiz. Differential effects of oral and intravenous L-carnitine on serum lipids: is the microbiota the answer? *Clin Kidney J* 2014; 7: 437–441)

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