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【 EDITORIAL 】

Effects of Levocarnitine Treatment on the Cardiac Function in Hemodialysis Patients

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Patients with hemodialysis (HD) are known to have carnitine deficiency (1). This may contribute to clinical disorders, including cachexia, dyslipidemia, erythropoiesis stimulating agent-resistant anemia, insulin resistance and glucose intolerance, muscle weakness, and myopathy as well as to intradialytic symptoms such as muscle cramps, hypotension, and cardiac arrhythmia. Free carnitine levels decrease principally as a result of dialytic loss, whereas decreased renal clearance and impaired β-oxidation of fatty acids lead to the accumulation of acylcarnitine and an abnormally high ratio of plasma acylcarnitine to free carnitine (1).

We previously reported that anemia, atherosclerosis, and the cardiac activity were improved by oral levocarnitine therapy while anemia was improved by intravenous levocarnitine therapy in HD patients (2, 3). Kaneko et al. reported that levocarnitine therapy improved cardiac dysfunction via the amelioration of the abnormal myocardial fatty acid metabolism (4). Echocardiographic measurements of the cardiac activity have been performed on dialysis patients to study the effect of chronic oral supplementation of levocarnitine; the results showed a statistically significant improvement in the systolic and diastolic function of the left ventricle (5). Sakurabayashi et al. reported that the myocardial washout of ^{123}I labeled β-methyl-*p*-iodophenyl-pentadecanoic acid (BMIPP), a fatty acid analogue used to examine myocardial metabolism, decreased in patients on long-term HD and was restored by levocarnitine therapy (6). The washout of BMIPP from the heart also decreases after the disturbance of mitochondrial carnitine acyltransferase 1 by tetradecylglycidic acid administration (6, 7). These results suggest that, in patients undergoing HD, carnitine deficiency disturbs myocardial fatty acid metabolism and may induce myocardial lipid accumulation. A decreased free carnitine concentration results in disturbed fatty acid transport into mitochondria; subsequently, the mitochondrial accumulation of acylcarnitine perturbs key enzymes of energy production and ATP transport. Therefore, ameliorating the myocardial fatty acid metabolism and acyl/free carnitine ratio due to levocarnitine treatment might help improve the left ventricular ejection fraction (LVEF) and reduce the left ventricular mass index (LVMI).

Cardiac disease is a major problem among dialysis patients, accounting for approximately half of all deaths in this patient population. Several studies have investigated the effect of levocarnitine administration on the cardiac function, with the findings summarized in the included Table (3, 6, 8-17). A significant correlation between the LVEF and endogenous levocarnitine levels has been reported, with these patients exhibiting considerable improvement in the LVEF after administration of levocarnitine for three months, a result that was particularly pronounced in patients experiencing recurrent hypotensive episodes (11).

Although mounting evidence supports the role of levocarnitine in the treatment of left ventricular dysfunction, other studies have obtained negative results (6, 9); however, the results of these studies should be interpreted with caution, as the patients in these studies had a normal baseline LVEF. We previously reported that the LVMI was an independent predictor of improvement in the LVEF following levocarnitine therapy. Furthermore, the responders to levocarnitine treatment were patients with left ventricular hypertrophy (LVH), as defined by the LVMI (3). Therefore, levocarnitine therapy is useful for hemodialysis patients with LVH; these patients may benefit from such therapy, with amelioration of the cardiac function and mitigation of the LVMI. The findings of these studies indicate that levocarnitine has great potential utility in the treatment of cardiac dysfunction, particularly in patients with LVH and dialysis-related hypotension.

Carnitine metabolism is an essential metabolite involved in fatty acid metabolism and the regulation of carbohydrate metabolism. However, this activity is altered during uremia.

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Table. Studies of the Effect of Levocarnitine on the Cardiac Function and Hypotension in Dialysis Patients.

Reference	Study design	Population	Dose and route	Treatment duration	Findings
8	Two-way, crossover, double-blind	9 HD patients	990 mg/day PO followed by placebo for 2 mo each	2 mo	↓Hypotension
		9 HD patients	Placebo followed by 990 mg/day PO for 2 mo each		
9	Two-way, parallel, double-blind	14 HD patients	2 g/Dx, IV	6 weeks	No difference in the cardiac function
		14 HD patients	Placebo		
10	Two-way, parallel, double-blind	38 HD patients	20 mg/kg per Dx, IV	6 mo	↓Hypotension
		44 HD patients	Placebo		
11	One-way, open-label	13 HD patients	1 g/Dx, IV	3 mo	↑LVEF T_0: 42.4% T_3: 48.6%
12	Two-way, parallel, open-label	25 HD patients	1 g/Dx, IV and 1 g/non-Dx PO	36 mo	↑LVEF
		35 HD patients	No treatment		↓LVEDV
6	One-way, open-label	11 HD patients	1 g/day PO followed by 0.5 g/day PO for 1 mo each	2 mo	↔ LVEDD, LVFS
					↑Cardiac scintigraphy
13	One-way, open-label	9 HD patients (impaired LVEF)	500 mg/day, PO	6 mo	↑LVEF T_0: 44.9% T_6: 53.8%
					↓CTR
14	One-way, open-label	11 HD patients	1 g/Dx, IV	8 mo	↑LVEF T_0: 32.0% T_8: 41.8%
15	Two-way, parallel, open-label	10 HD patients	10 mg/kg/day, PO	12 mo	↓LVMI
		10 HD patients	No treatment		
16	Two-way, parallel, double-blind	20 HD patients	1,500 mg/day, PO	6 mo	No difference in the cardiac function
		35 HD patients	No treatment		
17	Two-way, parallel, double-blind	10 HD patients	900 mg/day, PO	3 mo	↑LVEF T_0: 61.8% T_3: 64.4%
		8 HD patients	Placebo		↓Hypotension
3	Two-way, parallel, open-label	75 HD patients	20 mg/kg/day, PO	12 mo	↑LVEF T_0: 53.1% T_{12}: 58.6%
		73 HD patients	No treatment		↓LVMI

CTR: cardiothoracic ratio, Dx: dialysis session, HD: hemodialysis, IV: intravenous injection, LVEDD: left ventricular end-diastolic dimension, LVEDV: left ventricular end-diastolic volume, LVFS: left ventricular fractional shortening, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, mo: months, PO: per os (orally), T: treatment duration

The combination of uremia-induced LVH and carnitine deficiency contributes to the altered myocardial metabolism and impaired cardiac function. Levocarnitine treatment may partially ameliorate this uremic hypertrophy as well as exert beneficial effects on metabolism. Further large-scale clinical studies are necessary to ascertain whether or not this therapy has a significant effect on reducing the rates of cardiac mortality and morbidity.

Author's disclosure of potential Conflicts of Interest (COI).
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