MEDWIN PUBLISHERS
Committed to create value for Researchers

Open Access Journal of Urology & Nephrology

L-Carnitine and Cardiac Function in Chronic Hemodialysis

Yasuo Kudoh*

Kidney Center, Sapporo South One Hospital, Sapporo, Japan

Mini Review

Volume 1 Issue 1

Received Date: July 11, 2016

Published Date: July 18, 2016

***Corresponding author:** Yasuo Kudoh, Kidney Center, Sapporo South One Hospital, S1W13, Chuou-ku, Sapporo, Japan, Tel: 060-0061; Email: yasuo0302@view.ocn.ne.jp

Abstract

Carnitine supplementation has been accepted worldwide, as the treatment of secondary carnitine deficiency in the patients with chronic hemodialysis. However, the relationship between l-carnitine supplementation and the improvement of cardiac function in such patients has not been clarified clinically, although the positive relationship has been strongly speculated theoretically. In this mini-review, the pit-fall in past studies and the possibility of future clinical trial will be discussed.

Introduction

L-carnitine plays an essential role for lipid metabolism as a transporter of acyl-CoA compounds into mitochondria, especially in skeletal and cardiac muscle tissues, which rely on fatty acids as an energy source under aerobic metabolic conditions [1]. Therefore, it is supposed that carnitine depletion might produce severe tissue damage in heart and muscle. In animal model [2-4], it has been shown that the mice with congenital carnitine deficiency die of a cardiac insufficiency by 3-4 weeks after birth. In human [5,6], it has been reported that inherited systemic carnitine deficiency might be one of the causes of familial cardiomyopathy.

It is well known [7-10] that both plasma and tissue concentrations of carnitine in the patients with chronic hemodialysis decreased severely due to its impaired synthesis in kidney and great losses across the dialysis membrane during hemodialysis. It is reported [11] that CTR (cardio-thoracic ratio) was inversely related to plasma carnitine concentration in chronic hemodialysis patients. Therefore, the relationship between carnitine supplementation and improvement of cardiac function in these patients has been highly expected.

Clinical trial

Despite many clinical trials, the results regarding the effects of carnitine supplementation on cardiac function in chronic hemodialysis patients are controversial [10,12-14]. Some authors noted an improvement [15-19], while others found no change [20-22]. Because some studies were not adequately controlled nor the patient populations were not the same in the various studies, conclusion about the clinical effectiveness of carnitine cannot be drawn across these studies. Therefore, a national coverage on the use of carnitine for the improvement of cardiac function in end-stage renal disease patients was not approved in USA (2003) (Table 1).

Since then, the knowledge concerning about the suitable subjects (especially hemodialysis duration) [23], administration method (oral or intravenous) [24], optimal drug dosage and duration [25], and the accuracy of outcome evaluation (inter-dialytic, before or after dialysis) [26] have been accumulated. Recently, double blind randomized trial and open parallel control studies are published. It is reported that EF (ejection fraction) increased significantly from 61.8 to 64.4% (after 3 months) in one study[27], and 53.1 to 55.5% (after 6 months), to 59.6% (after 12 months) in another study

[28]. It might be reasonable to conclude that the carnitine supplementation have some beneficial effects on cardiac function, even which is supposed to be within normal range, in chronic hemodialysis patients.

An issue in the future

It must be a best way that carnitine is supplied to all hemodialysis patients with secondary carnitine deficiency. However, the wall of the expense stands in the way [29]. The patients, in whom main cause of cardiac dysfunction is carnitine depletion, should be the most suitable candidates of the supplementation. Question is how to select these patients. One of the key factors might be A/F carnitine ratio (acyl and free carnitine ratio). The accumulation of acyl compounds may reflect the severity of tissue metabolic disorders. It is demonstrated that the A/F carnitine ratio is positively related with cardiac mass index, and negatively related with EF in chronic hemodialysis patients [30]. Therefore, it might be speculated that a relative low A/F carnitine ratio means reversible mild damage of the tissue with carnitine depletion. It is also reported recently [31,32] that a low A/F carnitine ratio indicates a better tendency to erythropoietin responsiveness after carnitine supplementation. However, further examination must be waited to answer the question of which patients would benefit from and should receive l-carnitine.

Author	Year	Study Design	Sample Number	Mode/Duration	Outcome
Van Es	1992	Open	16HD	1g i.v/3 months	+
Sakurabayashi	1999	Open	11HD	0.5-1g p.o/2 months	-
Matsumoto	2000	Open	9HD	500mg p.o/6 months	+
Romagnoli	2002	Open	11HD	1g i.v/8 months	+
Fricke	1988	Open parallel control	8HD 16control	20mg/kg i.v/2 months	-
Trovato	1998	Open parallel control	25HD 35control	1g iv and 1g p.o/3 years	+
Higuchi	2015	Open parallel control	75HD 73control	20mg/kg p.o/12 months	+
Fagher	1985	Placebo control double blind	28HD	2g iv/6 weeks	-
Kudoh	2013	Placebo control double blind	18HD	900mg p.o/3 months	+

－Negative result, + Positive result

Table1: Comparison of studies concerning the effect of l-carnitine on cardiac function in dialysis patients.

References

1. Kudoh Y, Aoyama S, Torii T, Chen Q, Nagahara D, et al. (2014) The effects of oral L-carnitine supplementation on physical capacity and lipid metabolism in chronic hemodialysis patients. Nephron Extra 4(1): 33-41.

2. Horiuchi M, Yoshida H, Kobayashi K, Kuriwaki K, Yoshimine K, et al. (1993) Cardiac hypertrophy in juvenile visceral steatosis (jvs) mice with systemic carnitine deficiency. FEBS Lett 326(1-3): 267-271.

3. Koizumi T, Nikaido H, Hayakawa J, Nonomura A, Yoneda T (1988) Infantile disease with microvesicular fatty infiltration of viscera spontaneously occurring in the C3H-H-2(0) strain of mouse with similarities to Reye's syndrome. Lab Anim 22(1): 83-87.

4. Miyagawa J, Kuwajima M, Hanafusa T, Ozaki K, Fujimura H, et al. (1995) Mitochondrial abnormalities of muscle tissue in mice with juvenile visceral steatosis associated with systemic carnitine deficiency. Virchows Arch 426: 271-279.

5. Tripp ME, Katcher ML, Peters HA, Gilbert EF, Arya S, et al. (1981) Systemic carnitine deficiency presenting as familial endocardial fibroelastosis: a treatable cardiomyopathy. N Engl J Med 305: 385-390.

6. Waber LJ, Valle D, Neill C, DiMauro S, Shug A (1982) Carnitine deficiency presenting as familial cardiomyopathy: a treatable defect in carnitine transport. J Pediatr 101: 700-705.

7. Bonomini M, Zammit V, Pusey CD, De Vecchi A, Arduini A (2011) Pharmacological use of L-carnitine in uremic anemia: has its full potential been exploited? Pharmacol Res 63: 157-164.

8. Kudoh Y, Shoji T, Oimatsu H, Kikuchi K, Imura O, et al. (1984) [Plasma l-carnitine in patients with chronic hemodialysis. II. Pharmacokinetics of l-carnitine and its replacement therapy in these patients]. Nihon Jinzo Gakkai Shi 26: 195-202.

9. Reuter SE, Evans AM (2012) Carnitine and acylcarnitines: pharmacokinetic, pharmacological and clinical aspects. Clin Pharmacokinet 51: 553-572.

10. Schreiber B (2005) Levocarnitine and dialysis: a review. Nutr Clin Pract 20: 218-243.

11. Kudoh Y, Shoji T, Oimatsu H, Yoshida S, Kikuchi K, et al. (1983) The role of L-carnitine in the pathogenesis of cardiomegaly in patients with chronic hemodialysis. Jpn Circ J 47: 1391-1397.

12. Ahmad S (2001) L-carnitine in dialysis patients. Semin Dial 14: 209-217.

13. Pauly DF, Pepine CJ (2003) The role of carnitine in myocardial dysfunction. Am J Kidney Dis 41: S35-43.

14. Reuter SE, Faull RJ, Evans AM (2008) L-carnitine supplementation in the dialysis population: are Australian patients missing out? Nephrology (Carlton) 13: 3-16.

15. Khoss AE, Steger H, Legenstein E, Proll E, Salzer-Muhar U, et al. (1989) [L-carnitine therapy and myocardial function in children treated with chronic hemodialysis]. Wien Klin Wochenschr 101: 17-20.

16. Matsumoto Y, Sato M, Ohashi H, Araki H, Tadokoro M, et al. (2000) Effects of L-carnitine supplementation on cardiac morbidity in hemodialyzed patients. Am J Nephrol 20: 201-207.

17. Romagnoli GF, Naso A, Carraro G, Lidestri V (2002) Beneficial effects of L-carnitine in dialysis patients with impaired left ventricular function: an observational study. Curr Med Res Opin 18: 172-175.

18. Trovato GM, Iannetti E, Murgo AM, Carpinteri G, Catalano D (1998). Body composition and long-term levo-carnitine supplementation. Clin Ter 149: 209-214.

19. van Es A, Henny FC, Kooistra MP, Lobatto S, Scholte HR (1992) Amelioration of cardiac function by L-carnitine administration in patients on haemodialysis. Contrib Nephrol 98: 28-35.

20. Fagher B, Cederblad G, Monti M, Olsson L, Rasmussen B, et al. (1985) Carnitine and left ventricular function in haemodialysis patients. Scand J Clin Lab Invest 45: 193-198.

21. Sakurabayashi T, Takaesu Y, Haginoshita S, Takeda T, Aoike I, et al. (1999) Improvement of myocardial fatty acid metabolism through L-carnitine administration to chronic hemodialysis patients. Am J Nephrol 19: 480-484.

22. Topaloglu R, Celiker A, Saatci U, Kilinc K, Bakkaloglu A, et al. (1998) Effect of carnitine supplementation on cardiac function in hemodialyzed children. Acta Paediatr Jpn 40: 26-29.

23. Kudo Y, Shoji T, Oimatsu H, Yoshida S, Kikuchi K, et al. (1983) [Study on the risk factors of ischemic heart disease in patients with chronic hemodialysis, with special reference to the role of plasma l-carnitine]. Nihon Jinzo Gakkai Shi 25: 429-438.

24. Kudoh Y, Aoyama S, Torii T, Chen Q, Nagahara D, et al. (2014) L-carnitine kinetics in chronic hemodialysis patients: comparison between oral and intravenous supplementation. J Biochem Pharmacol Res 2: 117-124.

25. Kudoh Y (2015) Re-evaluation of l-carnitine in chronic hemodialysis. J Nephrol Res 2: 49-60.

26. Kudoh Y, Satoh S, Tsuchida A, Hikita S, Sasa Y, et al. (1988) The dual effects of hemodialysis on cardiac function assessed by pulsed Doppler

echocardiography. Jpn Circ J 52: 13-20.

27. Kudoh Y, Aoyama S, Torii T, Chen Q, Nagahara D, et al. (2013) Hemodynamic stabilizing effects of L-carnitine in chronic hemodialysis patients. Cardiorenal Med 3: 200-207.

28. Higuchi T, Abe M, Yamazaki T, Okawa E, Ando H, et al. (2016) Levocarnitine Improves Cardiac Function in Hemodialysis Patients With Left Ventricular Hypertrophy: A Randomized Controlled Trial. Am J Kidney Dis 67: 260-270.

29. Steinman TI, Nissenson AR, Glassock RJ, Dickmeyer J, Mattern WD, et al. (2003) L-carnitine use in dialysis patients: is national coverage for supplementation justified? What were CMS regulators thinking--or were they? Nephrol News Issues 17: 28-30, 32-24, 36 passim.

30. Kudoh Y, Aoyama S, Torii T, Chen Q, Takagi S, et al. (2016) The role of acyl/free carnitine ratio on uremic cardiomyopathy in chronic hemodialysis patients. Nova Science Publisher 103

31. Kudoh Y, Aoyama S, Torii T, Chen Q, Nagahara D, et al. (2014) Long-term effects of oral L-carnitine supplementation on anemia in chronic hemodialysis. Cardiorenal Med 4: 53-59.

32. Reuter SE, Faull RJ, Ranieri E, Evans AM (2009) Endogenous plasma carnitine pool composition and response to erythropoietin treatment in chronic haemodialysis patients. Nephrol Dial Transplant 24: 990-996.