L-Carnitine and Cardiac Function in Chronic Hemodialysis

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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 pitfalls 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.
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.

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