Carnitine in Renal Disease and Dialysis

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INTRODUCTION

- **Carnitine deficiency may be a significant problem in patients with kidney disease, particularly in those undergoing maintenance dialysis.**

Role of carnitine in intermediary metabolism

Carnitine is an important intermediary in fat metabolism.

- It shuttles long-chain fatty acids, in the form of acylcarnitines, into mitochondria for beta-oxidation.

- **Formula**: $C_7H_{15}NO_3$

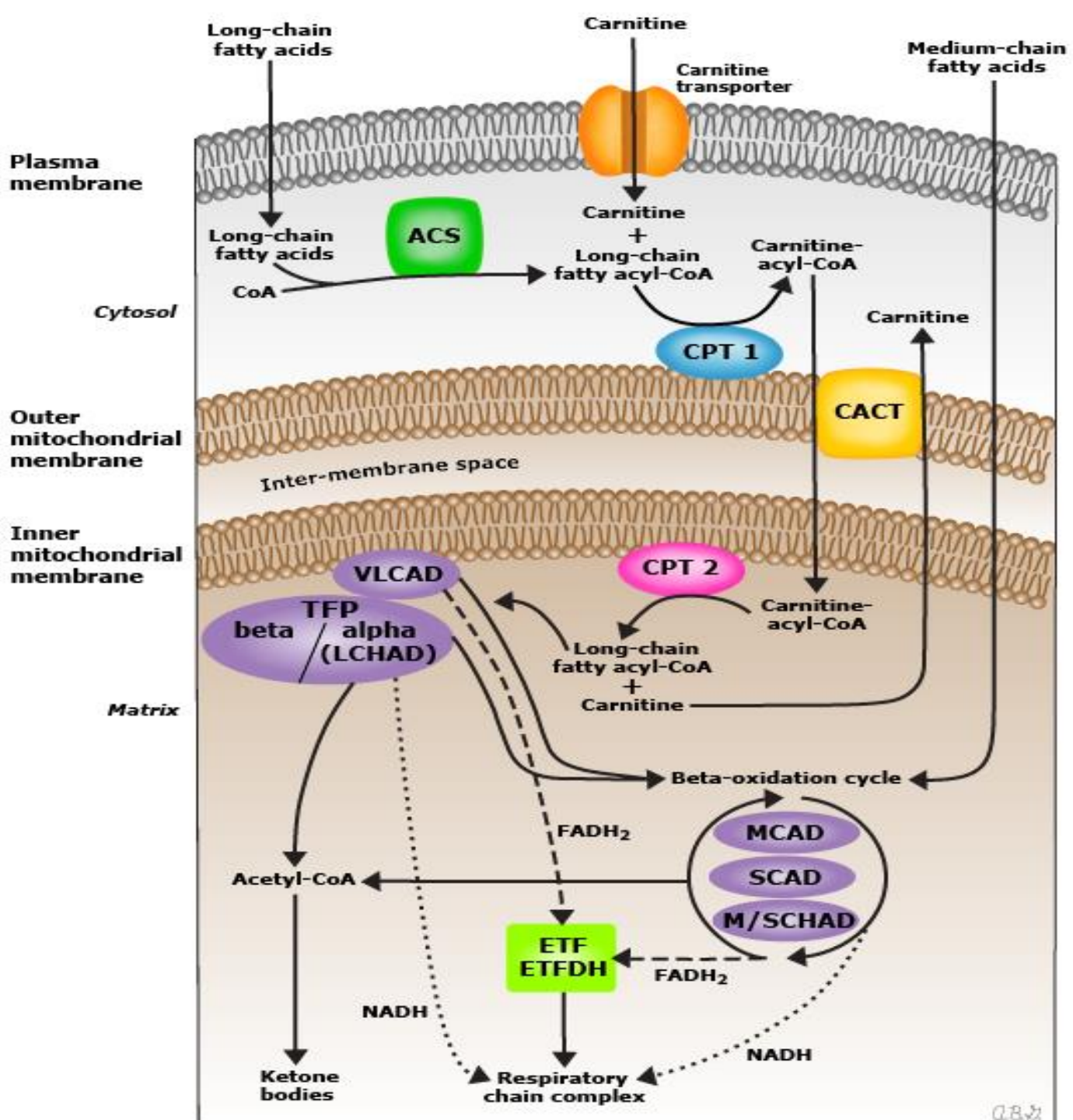
Role of carnitine in intermediary metabolism

- **Carnitine** crucial for **energy production** in tissues dependent upon fatty acid oxidation, such as **cardiac and skeletal muscle**.

Reactions of carnitine with activated fatty acids (acyl CoA):

- Acyl CoA + **carnitine** → **acylcarnitine** + CoASH

ACS: acyl-CoA synthetase; CPT 1: carnitine palmitoyltransferase 1; CACT: carnitine-acylcarnitine translocase; CPT 2: carnitine palmitoyltransferase 2; VLCAD: very-long-chain acyl-CoA dehydrogenase; TFP: trifunctional protein; LCHAD: long-chain 3-hydroxyacyl-CoA dehydrogenase; MCAD: medium-chain acyl-CoA dehydrogenase; SCAD: short-chain acyl-CoA dehydrogenase; M/SCHAD: medium/short-chain 3-hydroxyacyl-coenzyme A dehydrogenase; FADH2: flavin adenine dinucleotide; ETF: electron transfer flavoprotein; ETFDH: electron transfer flavoprotein dehydrogenase; NADH: nicotinamide adenine dinucleotide.



Role of carnitine in intermediary metabolism..

Functions of carnitine:

1. Fatty acid oxidation
2. Modulating the concentration of CoA,
3. Scavenging toxic acyl groups,
4. Facilitating their transport out of mitochondria.

Renal Handling and Metabolism of Carnitine in Renal Failure

While carnitine is derived from red meat and dairy products in the diet, biosynthesis in the liver, kidney, and brain is adequate to meet normal requirements in healthy individuals.

Approximately 95 percent of carnitine is stored in muscle, where it is concentrated by a specific transporter.

Free carnitine is filtered at the glomerulus, and over 90 percent undergoes tubular reabsorption.

Renal Handling and Metabolism of Carnitine in Renal Failure

By contrast, renal tubular absorption of acylcarnitine is limited, and clearance of acylcarnitine is four to eight times greater than that of free carnitine.

Esterification with carnitine is a pathway for detoxification and elimination of toxic acyl groups.

Renal Handling and Metabolism of Carnitine in Renal Failure

Alterations in chronic kidney disease (CKD)

- **Clearance** of both free carnitine and acylcarnitine **is reduced**.
- Plasma levels of free and total **carnitine** are **unchanged**, but serum acylcarnitine rises inverse to the decline of GFR.
- The ratio of acylcarnitine to free carnitine is markedly increased.

Renal Handling and Metabolism of Carnitine in Renal Failure

Metabolism in hemodialysis

- Plasma total carnitine concentration is normal or elevated;
- The free carnitine concentration is reduced and significantly lower than in healthy controls or in CKD;
- The acylcarnitine concentration is markedly increased,
- The ratio of acyl to free carnitine (AC:FC) is markedly increased (0.77 to 0.96) compared with healthy controls

Renal Handling and Metabolism of Carnitine in Renal Failure-

Factors contribute to this abnormal profile

1. Loss of renal parenchyma removes a source of endogenous carnitine synthesis.
2. Low dietary intake of **meat and dairy products** deprives patients of a rich source of carnitine.
3. Free carnitine clearance by hemodialysis is greater than acylcarnitine. This pattern is the reverse of normal urinary carnitine excretion.
4. Incompletely metabolized **acyl residues accumulate** and drive the formation of **acylcarnitine** esters.
5. The normal preferential renal excretion of acylcarnitine is lost in renal failure.

Peritoneal dialysis: **acylcarnitine is elevated.**

Carnitine deficiency and dialysis patients

- An AC:FC ratio >0.4 indicates a disorder of fatty acid metabolism
- Conversion to intensive (nocturnal) hemodialysis (five to six sessions per week, eight hours per treatment) reduced free and acylcarnitine levels and improved (reduced) the AC:FC ratio.

Carnitine deficiency and dialysis patients

- The plasma carnitine profile does not predict whether effective carnitine deficiency exists.
- The vast majority (95 percent) of hemodialysis patients have low free plasma carnitine,
- But neither plasma total, free, or acylcarnitine nor their ratios predict clinical response to L-carnitine supplements.
- Tissue (muscle or erythrocyte) total carnitine levels sometimes correlate with clinically significant endpoints.

Carnitine deficiency and dialysis patients

- L-carnitine supplementation increases plasma total, free, and acylcarnitine levels;
- The AC:FC ratio falls (improves) **only moderately** and incompletely.
- Suggesting that carnitine continues to bind acyl residues that are present in excess in dialysis patients
- In a study of 21 patients, plasma L-carnitine levels decreased within the first few months of beginning hemodialysis, while levels in muscle continued to decline, even after one year of dialysis

Impact of hemodialysis on endogenous plasma and muscle carnitine levels in patients with end-stage renal disease. Kidney Int 2004; 66:1527

CLINICAL FEATURES OF CARNITINE DEFICIENCY

Inherited cases in children: **Without kidney disease**:

1. **Muscle weakness,**
2. **Acute encephalopathy,**
3. **Hepatic dysfunction,**
4. **Cardiomyopathy,**
5. **Nonketotic hypoglycemia,**
6. **Frequent infections,**
7. **Failure to thrive**

CLINICAL FEATURES OF CARNITINE DEFICIENCY

Dialysis patients :

due to disparity between carnitine availability and metabolic needs.

1. The ratio of acylcarnitine to free carnitine is increased.
2. Symptomatic **improvement requires pharmacologic doses** rather than physiologic replacement.

CARNITINE SUPPLEMENTATION IN DIALYSIS PATIENTS

It is difficult to clearly ascribe benefits with L-carnitine supplementation in dialysis patients because of the following:

- The symptoms of carnitine deficiency (including muscle weakness and cardiomyopathy) overlap with those of dialysis patients generally.
- Laboratory evidence of abnormal carnitine metabolism is ubiquitous in this population.
- The response to carnitine supplementation cannot be predicted from plasma carnitine profiles.

CARNITINE SUPPLEMENTATION IN DIALYSIS PATIENTS

Numerous studies supporting improvement of

- **Plasma lipid profile**
- **Exercise capacity and oxygen utilization**
- **Muscle strength**
- **Intradialytic symptoms**
- **Sense of well-being**
- **Hospitalization rate**
- **Inflammatory markers**
- **Protein metabolism**
- **Left ventricular hypertrophy and cardiac function**
- **Anemia**
- **Response to erythropoietin**

CARNITINE SUPPLEMENTATION IN DIALYSIS PATIENTS

Data about benefits :

- limited, uncontrolled, small in size.
- controlled, prospective studies but small size,
- Inclusion of patients independent of signs and symptoms of carnitine deficiency,
- Relatively short follow-up.

A growing literature supports benefits.

The evidence is unclear that L-carnitine supplementation in dialysis patients improves exercise capacity, cardiomyopathy, or intradialytic symptoms.

1- Protein and muscle catabolism and signs of inflammation

- Acyl CoA increases insulin resistance and generation of free radicals and lipid peroxidation products
- Suggests carnitine deficiency may contribute to muscle wasting in dialysis patients.
- Results from different trials have found that L-carnitine has beneficial effects on inflammation, the oxidative state, and protein metabolism in dialysis patients.

1- Protein and muscle catabolism and signs of inflammation..

L-carnitine supplementation may be considered in the patient with:

1. Muscle wasting
2. And/or inflammation, as defined by weight loss that is not otherwise explained,
3. High c-reactive protein level,
4. And/or decreasing anthropometric measures (eg, mid-arm muscle circumference).

2- Lipid metabolism

L-carnitine supplementation: increases fatty acid oxidation, reduces myocardial fatty acid retention.

There is no consensus on the effect of L-carnitine on hyperlipidemia (elevated triglycerides and reduced high-density lipoprotein [HDL] cholesterol) in hemodialysis patients.

A 2002 meta-analysis found no beneficial effect of L-carnitine on serum lipid profiles.

Effects of L-carnitine supplementation in maintenance hemodialysis patients: a systematic review. J Am Soc Nephrol 2002; 13:708

3-Exercise limitation and oxygen consumption

The ability of L-carnitine supplementation to improve exercise performance in patients receiving hemodialysis is unclear.

suggest that impairment of muscle energetics in some dialysis patients is due not only to carnitine deficiency, but to other defects in fatty acid metabolism, such as carnitine palmitoyl transferase deficiency.

4- Intradialytic complications

L-carnitine may improve cardiac and skeletal muscle energy metabolism, thereby possibly ameliorating intradialytic symptoms.

A 2008 meta-analysis: 193 patients found no effect of L-carnitine on intradialytic hypotension and only a tendency to ameliorate muscle cramps, (no statistical significance).

A 2012 randomized study after the meta-analysis: 92 hemodialysis patients showed no effect of L-carnitine supplementation on hypotensive episodes.

5- Quality of life

Clinical status and sense of well-being were significantly improved in one controlled trial but not in two other studies.

In a randomized, controlled trial of 50 patients studied for 24 weeks, L-carnitine supplementation improved short form-36 (SF-36) scores and reduced erythropoietin doses.

Another study: L-carnitine supplementation had no effect on the SF-36 scores and did not change erythropoietin responsiveness.

6-Hospitalization

The effect of carnitine supplementation on rates of hospitalization is unclear.

In 1998-2003, infusion of L-carnitine 1 g per session for at least 10 sessions in a month was associated with a statistically significant reduction of 10.8 percent in subsequent months' hospital days.

A causal relationship cannot be inferred.

It is important to note that no existing randomized trials have addressed this issue.

7- Anemia and response to erythropoietin

L-carnitine may be effective in patients with chronic kidney disease (CKD) and anemia.

low serum carnitine levels accelerated erythrocyte osmotic fragility and negatively influenced the efficacy ofrHuEPO.

L-Carnitine has been shown to increase hematocrits in non–rHuEPO-treated patients and reduce rHuEPO requirements in patients on maintenance rHuEPO therapy.

American Journal of Kidney Diseases,Vol 41, No 4, Suppl 4 (April), 2003: pp S27-S34

8- Cardiovascular effects

Small number trials: partial reversal of cardiomegaly, improvement of left ventricular EF, and reductions in cardiac arrhythmias and anginal episodes.

L-carnitine in large doses non dialysis: ameliorated left ventricular dilatation after myocardial infarction,.

148 hemodialysis with carnitine deficiency: oral L-carnitine, 20 mg/kg/day, increased ejection fraction and reduced left ventricular mass index.

8- Cardiovascular effects..

Oral carnitine is metabolized to trimethylamine (TMA) by gut micro-organisms, and TMA is methylated in the liver to trimethylamine-N-oxide (TMAO).

TMAO levels are associated with cardiovascular risk and increased mortality.

Treatment of Dialysis-related Carnitine Deficiency-1

Indications for treatment:

- severe dialysis-related hypotension refractory to standard therapies.

Treatment of Dialysis-related Carnitine Deficiency-2

National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) when standard therapy has not been effective:

- Muscle weakness and lack of functional well-being
- Decreased exercise capacity or low peak oxygen consumption
- Cardiomyopathy and low cardiac output
- Anemia of renal failure that is unresponsive to or requires large doses of erythropoietin

Treatment of Dialysis-related Carnitine Deficiency-3

- Because of potential toxicity, absence of proof of efficacy, cost, and inability to predict benefit from laboratory evidence of carnitine deficiency, we do not agree with routine use of L-carnitine in dialysis patients.
- The recommendation NKF-KDOQI: trial of L-carnitine administration, while of unproven efficacy, would at least do no harm.
- Recent studies: an association between increased cardiovascular risk and the L-carnitine metabolite trimethylamine-N-oxide (TMAO) suggest possible toxicity associated with carnitine.

Treatment of Dialysis-related Carnitine Deficiency-4

The NKF Carnitine Consensus Conference recommended:

the clinical response to L-carnitine at three-month intervals and discontinued if no clinical improvement within 9 to 12 months.

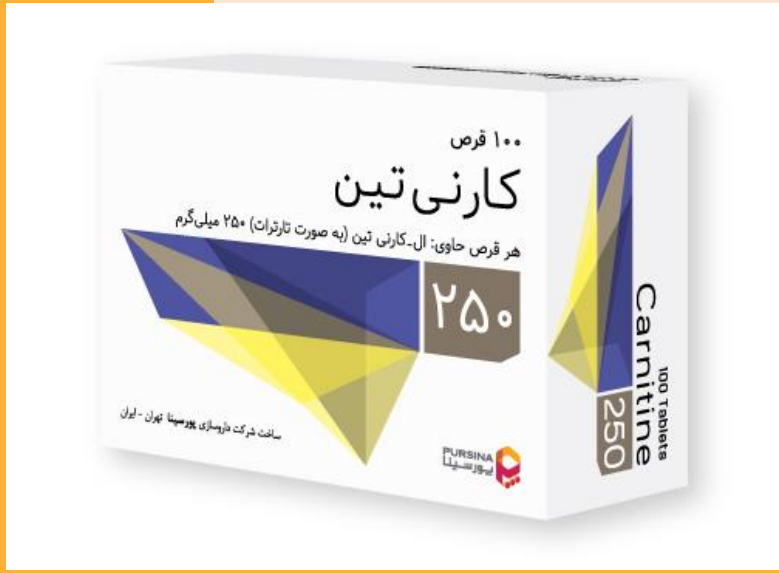
In our opinion, this interval should be reduced to three to six months.

Plasma carnitine levels to predict response has not been useful.

Carnitine products

1. Tab 250 mg , 330, 1000
2. Syr. 100mg/ml as 60ml or 120 ml.
3. Amp. 200 mg/ml 5 ml
4. Chew tab 1 gm
5. Oral solution 1gm/ 10 ml
6. Sach. 1 gm
7. Effer.
8. Powder

Carnitine products



L-carnitine dosing, route of administration, and toxicity

Because of the toxicity of D-carnitine, racemic mixtures of D- and L-carnitine should not be used.

FDA approved specifically the intravenous (IV) formulation of L-carnitine in dialysis patients.

A dose of 20 mg/kg IV after dialysis has been recommended.

Higher doses (up to 100 mg/kg) have been used,

but total doses >3 grams may increase platelet aggregation.

Lower doses (<5 mg/kg) have been used in treatment of hyperlipidemia

L-carnitine dosing, route of administration, and toxicity

L-carnitine is not routinely administered in peritoneal dialysate.

L-carnitine may be an effective glucose-sparing osmotic agent that enhances viability of mesothelial cells among peritoneal dialysis patients.

In a preliminary study of four patients receiving peritoneal dialysis for five days, equimolar L-carnitine was substituted for dextrose and yielded comparable if not superior ultrafiltration.

L-carnitine dosing, route of administration, and toxicity

Oral L-carnitine is not recommended:

- High oral doses are required because of limited bioavailability.
- Orally administered L-carnitine is converted to trimethylamine (TMA) by the intestinal microbiome and to TMAO in the liver.

L-carnitine dosing, route of administration, and toxicity

These toxic metabolites accumulate between dialysis sessions, even in patients who are not receiving oral L-carnitine supplements, but efficiently cleared by dialysis.

In dialysis patients who receive oral L-carnitine 1 g daily, plasma concentrations of TMAO continue to rise after two weeks.

TMA may cause cognitive impairment and malodorous breath characteristic of uremia, and TMAO has been associated with major adverse cardiovascular events and mortality.

L-carnitine dosing, route of administration, and toxicity

The safety of IV L-carnitine is not fully established.

It is unknown fraction of IV L-carnitine is converted to TMAO by intestinal bacteria.

Such conversion is plausible since there is enterohepatic circulation of L-carnitine.

TMAO is efficiently removed with dialysis.

Unknown whether its accumulation between dialysis sessions has any harmful effects

Summary-1

- Carnitine is an important intermediary in fat metabolism
- **Plasma carnitine** profile does not predict whether effective carnitine deficiency exists.
- An AC:FC ratio >0.4 indicates a disorder of fatty acid metabolism
- 95 percent of hemodialysis patients have low free plasma carnitine.
- **Carnitine** crucial for **energy production in cardiac and skeletal muscle.**
- Partial reversal of cardiomegaly, improvement of left ventricular EF.

Summary-2

Indications:

- Severe dialysis hypotension
- Muscle weakness
- Decreased exercise capacity
- Cardiomyopathy and low cardiac output
- Anemia of renal failure

➢ The clinical response to L-carnitine at three-month intervals and discontinued if no clinical improvement within 9 to 12 months.

Summary-3

- FDA approved intravenous (IV) formulation of L-carnitine in dialysis patients: A dose of 20 mg/kg IV after dialysis has been recommended.
- Oral L-carnitine is not recommended.
- Lower doses (<5 mg/kg) have been used in treatment of hyperlipidemia
- Plasma carnitine levels to predict response has not been useful.
- L-carnitine may be an effective glucose-sparing osmotic agent in PD.