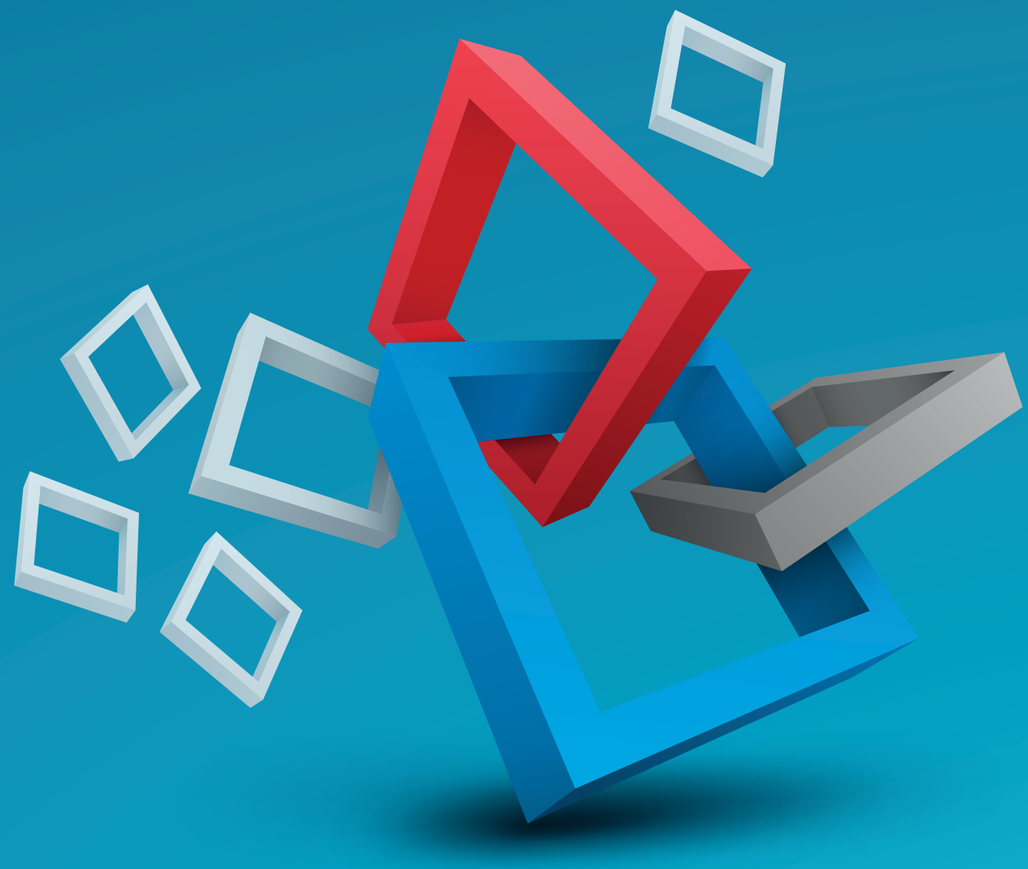
SPOTLIGHT
on **CARNITINE**

Clinical benefits of **L-carnitine supplementation in dialysis-related carnitine disorder** in ESRD patients



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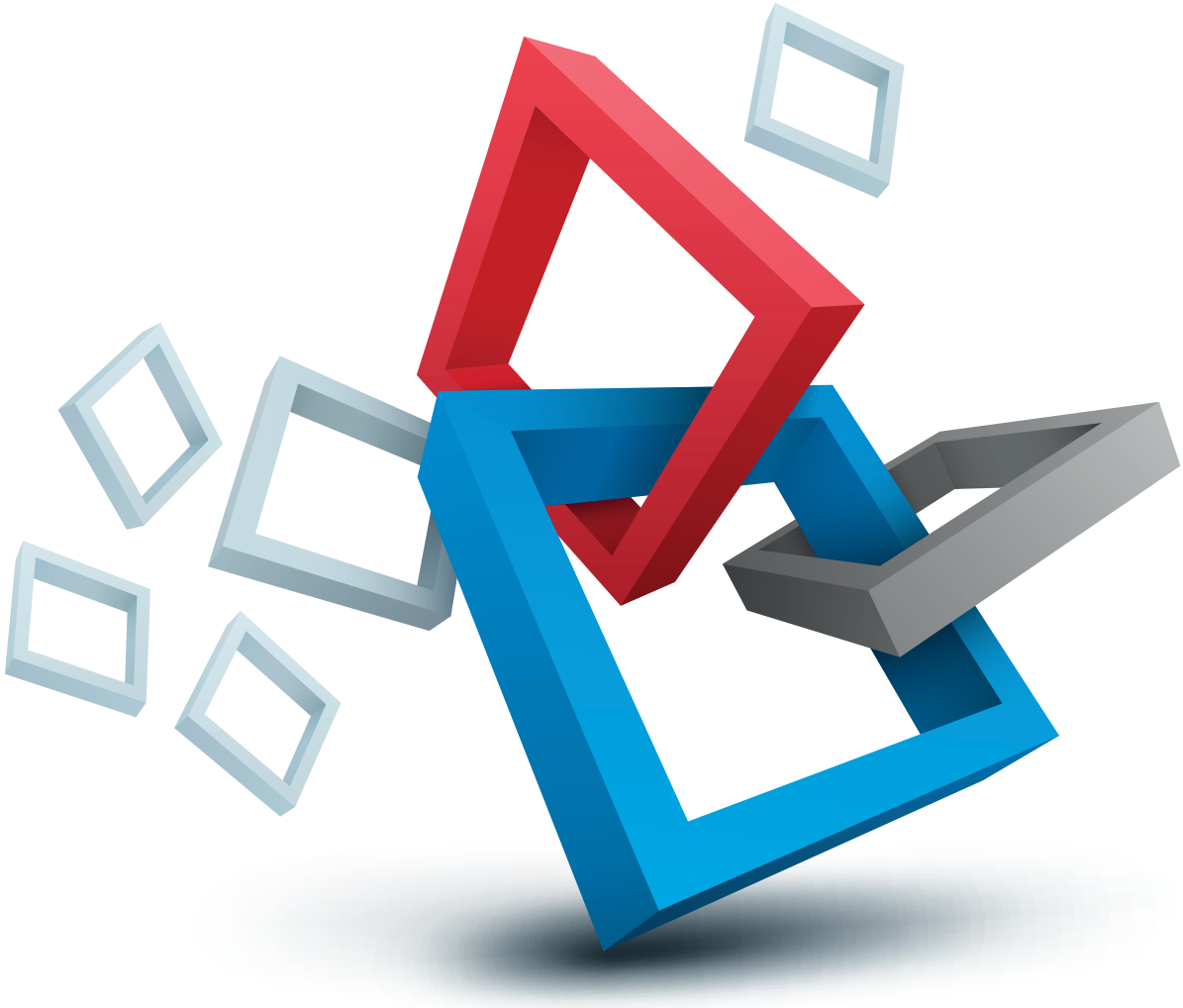

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Summary

Introduction

Carnitine is a low molecular weight polar compound that plays a critical role in fatty acid metabolism. The molecule exists as two enantiomers, D-carnitine and L-carnitine, the latter form being the active metabolite in humans. The hydroxyl group on the chiral carbon atom can form a range of different chain length esters, and reversible esterifications are catalyzed by membrane-bound carnitine acyltransferases that have different specificities and varying subcellular distribution patterns[1-5].

It is important to clarify here the carnitine terminology used in the literature. Free carnitine (or L-carnitine) refers to the non acylated form, while acyl-L-carnitine represents all of the short-, medium-, and long-chain esters involved in the transfer of acyl groups from acyl coenzyme A (CoA). Total carnitine is the sum of L-carnitine and all of its esters[4], sometimes referred to as "the carnitine pool". It is also important to note that short-term changes in plasma L-carnitine levels do not necessarily indicate alterations in the total body carnitine, given that the amount of carnitine in the plasma at any time is a very small fraction of the total body pool[4].

L-carnitine is widely distributed in nature, especially in red meats, fish and dairy products. In normal human omnivores (non-vegetarians), approximately 75% of L-carnitine is obtained from the diet. The percentage not obtained from food is synthesized endogenously from two essential amino acids, lysine and methionine. This occurs in kidney, liver and brain[6-8] **(Figure 1)**. Two sources of L-carnitine in humans are intestinal absorption from dietary sources and endogenous synthesis. Dietary intake can be up to 12 μmol/kg/day in adult omnivores[9,10]. Intestinal absorption is transport mediated, so the efficiency of absorption decreases with high oral loads[4].

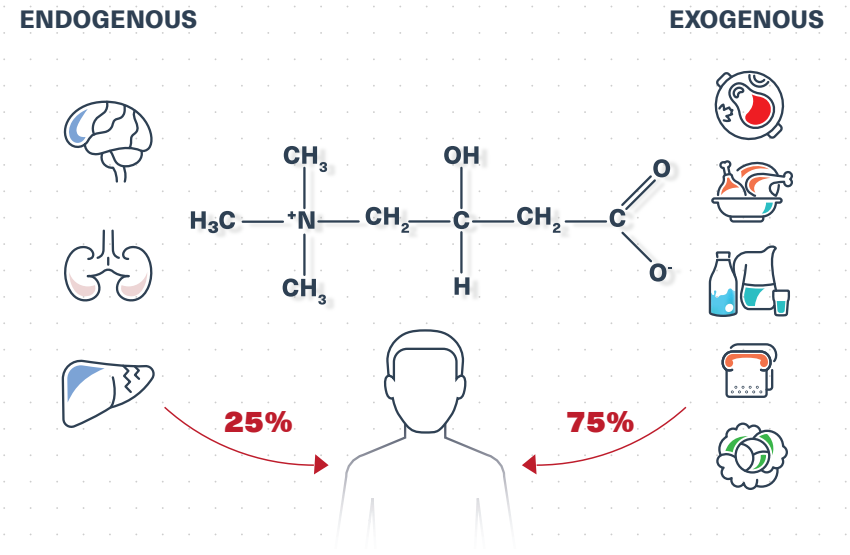


Figure 1. L-carnitine sources. [Adapted from (8)].

The carnitine pool has a physiologic role in the β-oxidation of long-chain fatty acids by catalyzing their transport into the mitochondrial matrix, modulating the cellular and mitochondrial ratio of acyl CoA to free CoA, transfer of acetyl and other short-chain acyl groups from peroxisomes to mitochondria, oxidation of branched-chain amino acids, reesterification of triacylglycerol in the endoplasmic reticulum before secretion as very low density lipoproteins, stabilization of cell membranes by removing long-chain

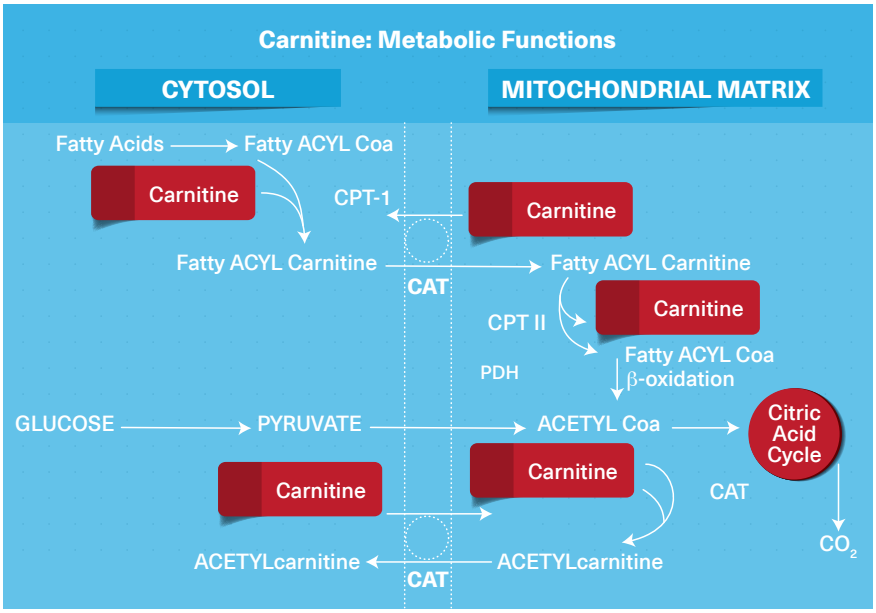


Figure 2. Metabolic functions of carnitine. CAT, carnitine acetyltransferase; CPT, carnitine palmitoyl transferase; PDH, pyruvate dehydrogenase; CO_2, carbon dioxide. [Adapted from (21)].

acyl CoAs, and removal of excess acyl groups from the body **(Figure 2)**[4,11-21].

Circulating fatty acids are transported into the cytoplasm in amounts determined principally by their plasma concentration. In order to be used for energy production, fatty acids must first be activated by complexing with coenzyme A (CoA), consuming adenine triphosphate (ATP), and being catalyzed by acyl-CoA-synthetase[21]. Though short and medium-chain acylCoA molecules are able to pass through the inner mitochondrial membrane without further modification, long-chain fatty acyl-CoAs are unable to pass through this barrier without the carnitine system. Carnitine palmitoyl transferase I, located on the inner side of the outer mitochondrial membrane, catalyzes the transfer of activated long-chain fatty acids between CoA and L-carnitine. Once bound to carnitine, the long-chain acyl group can pass through the inner mitochondrial membrane, where the reaction is reversed by carnitine palmitoyl transferase II to yield the respective long-chain acyl CoA (LCACoA) and carnitine. Imported by the carnitine system, the acyl-CoA is available for energy generation through β-oxidation and subsequent metabolism[21].

A second important function that is often overlooked and has been stressed in more recent work is that L-carnitine also serves to export unmetabolized acyl derivatives out of the mitochondrion as acylcarnitines. As described subsequently, a number of pathologic conditions are characterized by a reduction in the oxidation of fatty acyl groups. An important example of such a condition, frequently encountered in dialysis patients, is cardiac ischemia. Kobayashi and Fujisawa documented that acyl-CoA moieties accumulate in both the cytoplasm and mitochondria of ischemic dog hearts. When perfused with L-carnitine, the intracellular concentration of acyl-CoA species was reduced in a dose-dependent manner. Suzuki et al. had earlier shown a reduction in both acyl-CoA and acylcarnitines in ischemic dog hearts by administration of L-carnitine with a subsequent increase in myocardial ATP production. An additional important feature of both of these studies is that the carnitine-induced reduction of acyl-CoA and acylcarnitines was accompanied by a restoration of depressed levels of free CoA. This ability of carnitine to buffer the acyl:free CoA ratio and restore levels of available free CoA for further metabolic functions is recognized as a third important metabolic action of carnitine[21].

Given its essential role in metabolism, L-carnitine plasma and tissue levels are maintained within a narrow homeostatic range[4,11] that is controlled by gastrointestinal absorption, endogenous biosynthesis, renal tubular reabsorption, and compartmentalization through carrier-mediated transport

between plasma and tissues. L-carnitine is endogenously synthesized from trimethyllysine (using the essential amino acids lysine and methionine) in humans at a rate of 1-2 μmol/kg/day[3,11]. The enzyme responsible for the hydroxylation required in the last step of synthesis is only present in human kidney, liver, and brain, and hence L-carnitine cannot be synthesized in skeletal or heart myocytes[2], although skeletal myocytes contain 98% of the total carnitine pool[4]. Because L-carnitine is highly polar at physiologic pH, it does not readily cross the cell membrane, and high tissue:plasma concentration ratios (as in skeletal muscle) are maintained by carrier-mediated transport systems such as the sodium-dependent carnitine organic cation transporter (OCTN2), which also plays a role in L-carnitine renal tubular reabsorption[4,22]. In patients with primary carnitine deficiency, mutations in the OCNT2 gene lead to impaired muscle uptake and decreased renal tubular reabsorption[23].

In addition to carnitine synthesis, the kidney plays an important role in L-carnitine homeostasis and the maintenance of plasma L-carnitine concentrations within a narrow homeostatic range by saturable tubular reabsorption. Plasma L-carnitine is not protein bound and is freely filtered at the glomerulus. More than 95-99% of the filtered load undergoes transport-mediated tubular reabsorption[24-26], which decreases if the plasma concentration of L-carnitine is greater than 60 μmol/L, due to the saturation of transporters[25,27]. Renal clearance in isolated perfused rat kidney increases when perfusate concentrations exceed normal endogenous plasma concentrations as a consequence of saturation of tubular transport systems[25,28,29]. The saturable transport mechanism is further supported by human studies where fractional reabsorption of L-carnitine was reduced when vegetarians were given oral L-carnitine supplementation[4,23], and where administration of propionyl-L-carnitine hydrochloride caused significant increases in the renal clearances of propionyl-L-carnitine, L-carnitine, and acetyl-L-carnitine[25]. In addition, vegetarians were found to excrete markedly less L-carnitine than omnivores at plasma L-carnitine concentrations that were only 10-20% lower[9].

The kidney also plays a role in the esterification of L-carnitine and preferential excretion of short-chain carnitine esters. There is evidence that acetyl-L-carnitine formed locally in kidney from esterification of L-carnitine is secreted into the renal tubule possibly as a mechanism to excrete excess L-carnitine or acetyl groups[3,4]. In healthy adults, renal clearance of acetyl-L-carnitine was almost four times greater than that of L-carnitine, perhaps to maintain a high ratio of free L-carnitine to acyl-L-carnitine in plasma through preferential retention of L-carnitine[4,25]. The isolation of α-methyl medium-chain acylcarnitines in human urine further supports a role for the kidney in L-carnitine homeostasis[18].

CARNITINE IN HEMODIALYSIS PATIENTS

The kidney has an important effect on the metabolism of carnitine. In healthy individuals, carnitine is freely filtered and tubular resorption of free carnitine (FC) is almost complete; what appears in urine is carnitine ester, or acylcarnitine (AC). Thus in normal individuals the renal clearance of AC is four to eight times that of FC[30-32]. Deteriorating renal function is associated with decreased carnitine clearance and impairment of normal excretion of AC, leading to elevated plasma levels of carnitine. Thus uremic patients who are not yet on dialysis have increased levels of both FC and TC and markedly elevated concentrations of AC[31].

Unlike nondialyzed uremic patients, most hemodialysis (HD) patients exhibit relative carnitine deficiency, which is manifested as subnormal plasma/serum FC concentrations[31,33-39] and diminished muscle stores[32,40-45]. As with uremic patients, HD patients have markedly elevated AC levels[31,34,36,38] **(Figure 3)**.

HD patients demonstrate an abnormally high ratio of aryl to free carnitine[31,35,36,39,46]. An AC:FC ratio of greater than 0.40 indicates a relative FC de-

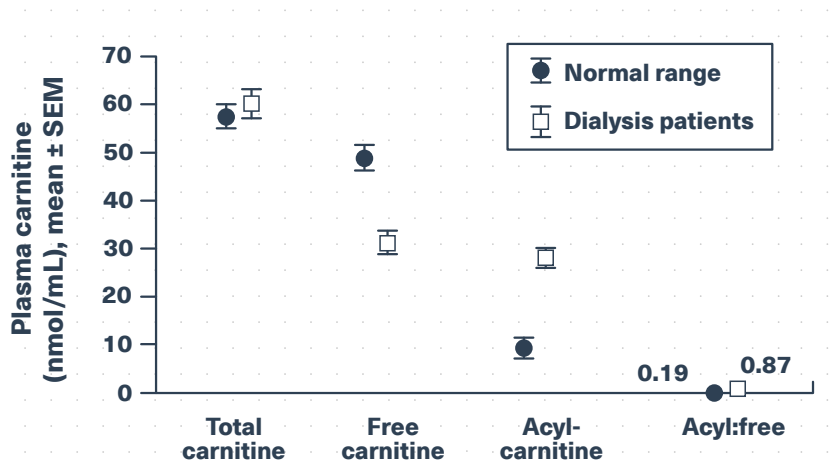


Figure 3. Plasma carnitine profile in HD patients and normal ranges. Values for total carnitine, free carnitine, acylcarnitine, and the ratio of acyl to free carnitine are shown (mean ± standard error of the mean). [Adapted from (36)].

ficiency (insufficiency); in normal patients the AC:FC ratio is approximately 0.19, while it is increased to 0.87 in HD patients[36]. Despite the abnormal carnitine fractions, most investigators report that the plasma concentration of TC in HD patients is normal[31,36,38,44,47] or decreased[34,40,45,47,48], whereas three investigators have reported elevated TC levels in HD patients[32]. The possible reasons for subnormal FC concentrations are included in **Table 1**.

Table 1. Potential factors contributing to carnitine depletion in HD patients. [Adapted from (49)].

Decrease availability	Increased requirements
Low dietary intake of carnitine-rich food (meat and dairy products)	Abnormal fatty acid metabolism
Decreased endogenous production of carnitine	
Nonselective dialytic losses (FC and AC)	

Carnitine is a small water-soluble molecule that is well dialyzed; during one HD session, plasma concentrations of carnitine declined as much as 75%[50]. This rapid decrease is quickly corrected by transport of carnitine from tissue stores, which may lead to a decrease in muscle carnitine levels[44,46]. One study showed that muscle carnitine content 6 hours after HD remained lower than predialysis concentrations[51]. Plasma levels of TC return to predialysis levels 6 hours after HD[44]. FC clearance by HD is greater than that of AC, a pattern that is the reverse of normal urinary carnitine excretion[46], which may contribute to decreases in FC concentration.

Increased clearance of L-carnitine by the dialysis procedure is due to its small molecular weight and very low binding to plasma proteins **(Figure 4)**. Unlike the kidney, the dialysis filter lacks the selectivity for preferential retention of free L-carnitine to acyl-L-carnitine and the ability to conserve L-carnitine when plasma levels decrease, resulting in the disruption of L-carnitine homeostasis[4]. It is observed that with initiation of dialysis, there is an increase in the acyl-L-carnitine:L-carnitine ratio in plasma, perhaps due to the greater molecular weight and increased lipophilicity of longer-chain acyl-L-carnitines resulting in lower dialysis clearance[4,52,53]. Plasma levels of acyl-L-carnitines were almost threefold greater and L-carnitine levels much lower in hemodialysis patients compared to age-matched controls[52,54]. While free L-carnitine comprised more than 88% of the total plasma L-carnitine in healthy adults (12% esterified), it comprised only 67% of the total carnitine in end-stage renal disease (ESRD) patients (33% esterified)[52]. In addition, acyl-L-carnitine:carnitine ratio positively correlated with increased months on maintenance hemodialysis[52,54].

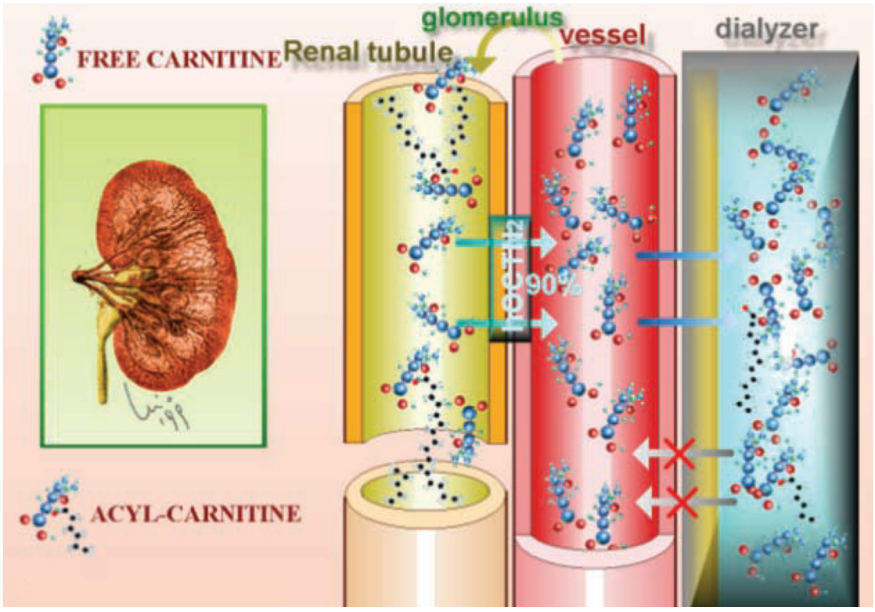


Figure 4. Mechanisms of transport of free carnitine and acyl-L-carnitine through the kidneys and evidence of free carnitine losses during hemodialysis sessions, because filters do not allow carnitine reabsorption. [Adapted from (55)].

L-carnitine deficiency, in fact, progresses with dialysis vintage (duration of dialysis); significant negative correlation has been found between dialysis duration (vintage) and plasma FC concentration **(Figure 5)**[52,56], as well as between months on dialysis and muscle carnitine content **(Figure 6)**[9]. Bazzi et al.[51] found that patients undergoing HD for more than 10 years had decreased muscle carnitine; this was not seen in patients who had been

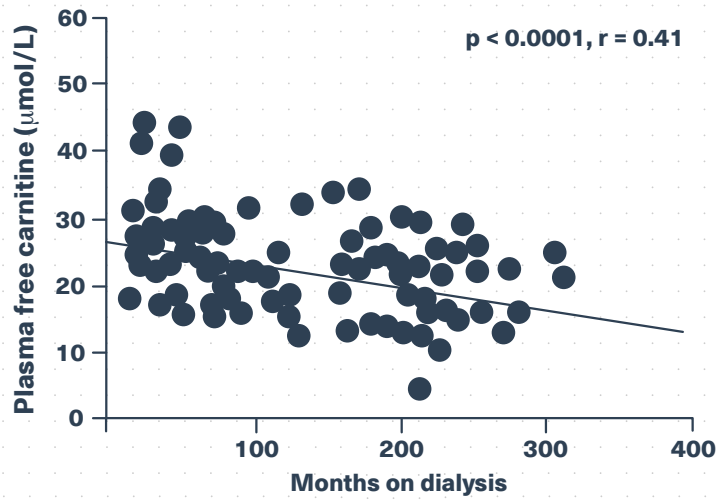


Figure 5. Correlation between dialysis vintage and free carnitine levels in 107 patients on HD. Each point represents an individual patient. [Adapted from (52)].

on HD for less than 3 years[51]. Significant reductions in predialysis TC levels with dialysis vintage have been documented as well. Over a 25-week period, Rodriguez-Segade et al.[34] found a gradual decrease in serum TC levels, and Kudoh et al.[33] documented a gradual reduction in predialysis plasma TC levels over a 2-year period. Older patients appear to be at greatest risk for carnitine deficiency; there is a significant negative correlation between serum FC levels and age[57]. There appears to be no relationship between carnitine deficiency and measures of dialysis adequacy[57].

Finally, fatty acid metabolism and the distribution of fatty acids are abnormal in dialysis patients[58]. Supplementation with carnitine tends to normalize fatty acid profiles. It is possible that because of abnormal fatty acid metabolism the need for carnitine increases, and the relative lack of FC (secondary to dialytic losses) may further contribute to the abnormal carnitine profile.

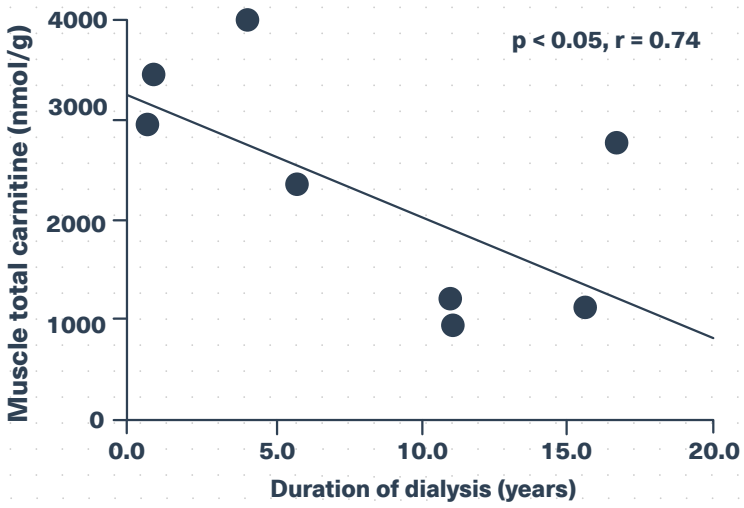


Figure 6. Correlation between dialysis vintage and muscle carnitine levels in patients on HD. Each point represents an individual patient. [Adapted from (9)].

CLINICAL MANIFESTATIONS OF DIALYSIS-RELATED CARNITINE DEFICIENCY AND EVIDENCE FOR CARNITINE SUPPLEMENTATION

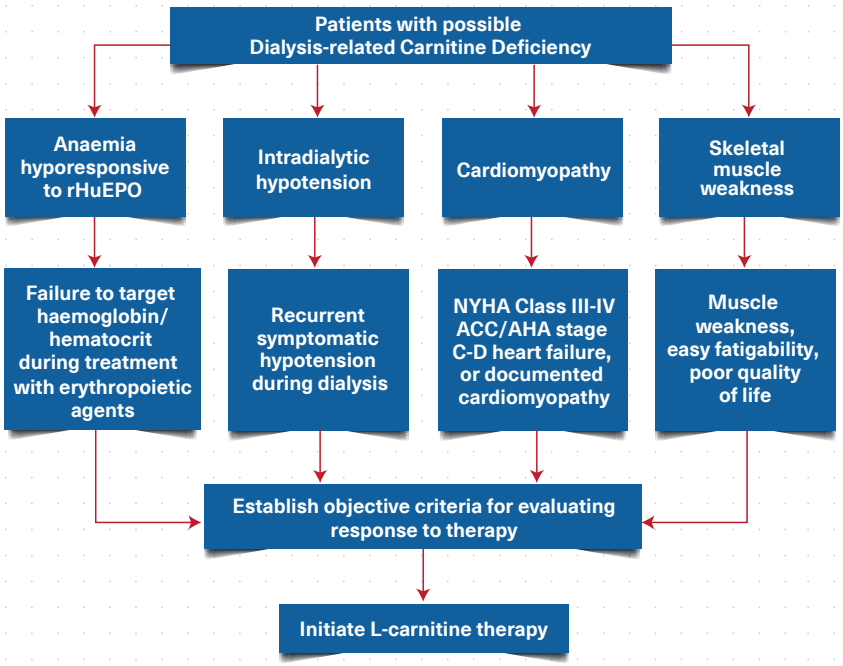
Given the vital role L-carnitine plays in fatty acid metabolism, and given the derangement observed in the carnitine system in ESRD patients prior to and after initiation of renal replacement therapy, many investigators advocated L-carnitine supplementation in order to alleviate several dialysis-related disorders. Underlying conditions for which a trial of L-carnitine treatment might be considered, such as intradialytic hypotension, heart failure, erythropoietin-resistant anemia, muscle weakness, and low exercise capacity, should be fully evaluated and standard therapy attempted prior to consideration of carnitine supplementation. The evidence that does exist for each of these indications is reviewed below.

Given the available evidence on the depletion of the carnitine pool in dialysis patients, several studies have evaluated the effects of repletion of carnitine stores, using both the systemic and oral administration routes, and in December 1999 the Food and Drug Administration has approved its use on the basis of plasma free carnitine levels, thus comparing the "serious and life threatening condition" of the deficit observed during dialysis to that found in patients with hereditary deficiency[59]. Many dialysis providers are probably unaware of this statement, and they might have never known of a patient who was being treated for carnitine deficiency. Even though many studies have confirmed that correcting carnitine deficiency can lead to improved response to erythropoietin, decreased intradialytic hypotension, improved quality of life and significant decreased hospitalizations, it is still rarely considered in the treatment of dialysis patients. The use of L-carnitine for intradialytic hypotension has also been described in 2007 European Best Practice Guidelines on Haemodialysis (EBPG), where is discussed that carnitine supplementation may be beneficial in patients with otherwise unexplained systolic dysfunction and intradialytic hypotension. Expert consensus panels of the American Association of Kidney Patients and of the National Kidney Foundation have consistently recommended its use in dialysis patients **(Figure 7)**[60,61].

Major United States insurance companies, notoriously restrictive in reimbursement policies, authorized L-carnitine use in patients with intradialytic hypotension or resistance to erythropoietin treatment in 2003[62].

Dialysis-related muscular symptoms, fatigue, and hypotension

L-carnitine is present in skeletal muscle tissue in very high levels and plays a vital role in the generation of energy through β-oxidation of fatty acids. It was



ACC/AHA = American College of Cardiology/American Heart Association;
NYHA = New York Heart Association; rHuEPO = recombinant human erythropoietin

Figure 7. Recommended approach to the evaluation and treatment of a patient with a possible dialysis-related carnitine deficiency. Patient should be evaluated for other possible causes and managed with standard therapies prior to diagnosis of dialysis-related carnitine deficiency. [Adapted from (60)].

proposed that some of the muscular symptoms reported by patients on maintenance hemodialysis may be related to carnitine deficiency. For example, in 30 chronic hemodialysis patients with muscle symptoms such as cramps, weakness, and fatigue, Sakurauchi et al.[63] reported significantly lower plasma free L-carnitine levels, and higher acyl-carnitine:free carnitine ratios in comparison to the levels in 21 such patients without muscle symptoms. A direct correlation was observed between carnitine levels and the mean diameter of type 1 skeletal muscle fibers in hemodialysis patients treated with L-carnitine[64]. Several studies have investigated the effects of L-carnitine in reducing dialysis-related muscle weakness and cramps, postdialysis fatigue, and intradialytic hypotension. These studies ranged in duration of therapy from 2 to 6 months and used different routes of L-carnitine delivery (intravenous and oral). In an uncontrolled but prospective study, after 3 months of therapy with L-carnitine (500 mg once a day orally), Sakurauchi et al.[63] reported a significant decrease in fatigue in 14 of 21 and improvement in muscle weakness in 14 of 24 hemodialysis patients. In a nonrandom, crossover study of 18 patients, Casciani et al.[65] reported a significant improvement in postdialysis asthenia. In another multicenter, double-blind study where 38 patients were randomized to therapy with L-carnitine (20 mg/kg intravenously after dialysis for 6 months) and 44 randomized to placebo, intradialytic hypotension and muscle cramps were reduced only in the carnitine arm[66]. In addition, midarm muscle area increased in the carnitine arm but remained unchanged in the placebo arm. Bellinghieri et al.[67] showed a correlation between blood and muscle levels of L-carnitine and reduced intradialytic asthenia and cramps after 60 days of oral therapy in a crossover, double-blind study of 14 hemodialysis patients. However, in another randomized double-blind study of 28 hemodialysis patients, therapy with 2 g intravenous L-carnitine three times a week for 6 weeks had no effect on several tests of muscular function or on subjective improvement in fatigue[68].

Low exercise capacity

Studies that assessed exercise capacity after administration of L-carnitine to maintenance dialysis patients were performed. Mioli et al.[69] showed an increase in maximum workload after 45 days of oral carnitine therapy.

Albertazzi et al.[70] reported subjective improvement in physical activity in 10 patients after oral carnitine therapy versus no change in 10 controls. A trend toward improvement in subjective physical activity that was not statistically significant was revealed in a double-blind placebo-controlled group of 14 hemodialysis patients after 6 months of therapy with 2 g intravenous L-carnitine three times a week[71]. In the multicenter, randomized placebo-controlled trial that reported a reduction in muscle cramps and intradialytic hypotension, maximal oxygen consumption measured during a progressive exercise test also improved significantly after 6 months of intravenous L-carnitine therapy ($p < 0.03$)[66]. There was a statistically insignificant trend toward increased exercise time in the carnitine arm. However, in another randomized double-blind study, although administration of intravenous L-carnitine for a duration of 6 weeks was associated with an improvement in maximum muscle strength above baseline[68].

Anemia

Anemia is a common and important complication among patients with chronic kidney disease and dialysis providers should be familiar with the best practices for its prevention and treatment. Untreated anemia places patients at risk for cardiovascular events, more rapid progression of renal disease, significantly decreased quality of life and death[72]. The most well-known cause of anemia is inadequate erythropoietin caused by a decreased release from diseased kidneys. However, as renal anemia is of multifactorial origin **(Figure 8)**, a considerable proportion of patients shows recombinant human erythropoietin hypo-responsiveness because of the presence of other etiological factors.

The relationship between dialysis-related L-carnitine disorder and anemia may be explained by the proposed role of L-carnitine in improvement of erythrocyte survival through enhanced erythrocyte membrane stability[73-77]. Matsumura et al.[44] found a significant inverse correlation between serum total carnitine levels and both erythrocyte fragility and weekly maintenance erythropoietin doses in 26 hemodialysis patients. Studies showed that L-carnitine supplementation in maintenance dialysis patients was associated with improved red blood cell deformability, membrane stability, and increased hematocrit[75-77].

There are several randomized placebo-controlled trials that evaluated the effect of L-carnitine on hemoglobin or hematocrit. One study was done prior to the availability of erythropoietin, and all patients received folate, vitamin B12, and sodium ferrigluconate at the end of each dialysis session, in addition to placebo or L-carnitine for 12 months[78]. The mean hematocrit decreased from 24.0% to 21.8% in the placebo arm and increased from 25.5% to 37.4% in the treatment arm. In another study, in 24 maintenance hemodialysis patients receiving recombinant erythropoietin therapy, hematocrit remained stable in the carnitine arm, but decreased significantly, although slightly (29.5% to 27.9%), in the placebo arm after 6 months of therapy (1 g intravenously after each dialysis)[79]. Patients were excluded if they had severe hyperparathyroidism, and about the same proportion received iron in each arm. Efforts were made to decrease the dose of erythropoietin without a decrease in hematocrit. Carnitine treatment was associated with a 38.1% reduction in erythropoietin requirements in the active arm (102.2 ± 52.6 U/kg/week versus 63.3 ± 37.8 U/kg/week, $p < 0.02$), while there was no change in erythropoietin requirements in the placebo arm. Lastly, in a randomized placebo-controlled study of 31 hemodialysis patients, a trial of 1 g intravenous L-carnitine after each dialysis resulted in a significant increase in hematocrit (mean 32.8% versus 28.1%) and a significant decrease in erythropoietin dose (mean 92.8 versus 141.3 U/kg/week) only in the subgroup of 21 patients who were older than 65 years of age[80]. Other studies in which the effect of carnitine therapy on anemia was addressed were either non-randomized or suffered from a lack of statistical power[67,81]. Based on this

Figure 8. Combination of multiple factors responsible of developing anemia in Chronic Kidney Disease. [Adapted from (24)].

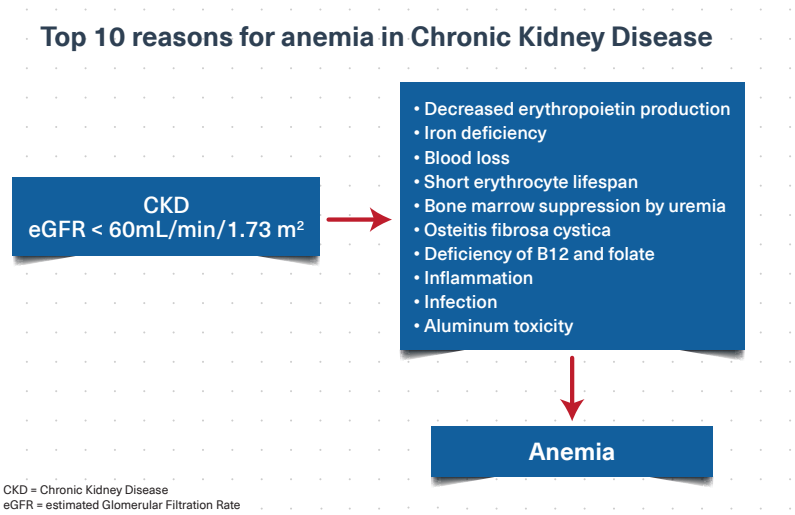
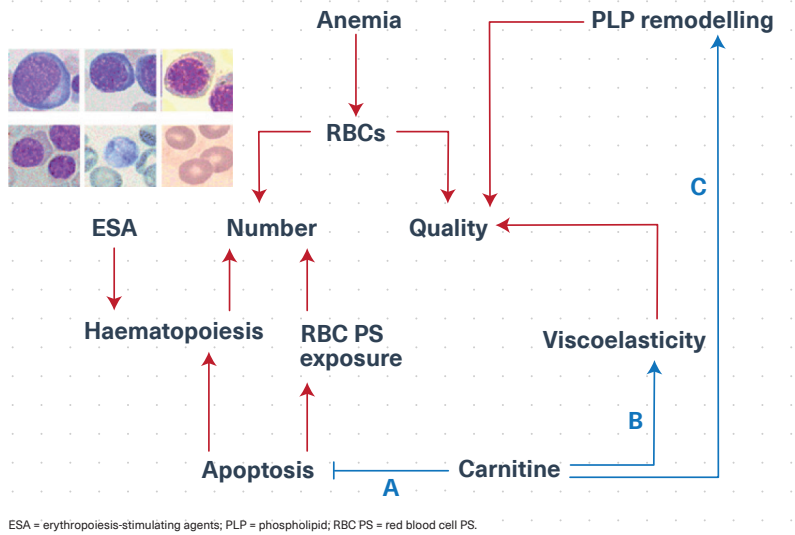


Figure 9. Multiple modes of action through which L-carnitine may affect the number and quality of red blood cells in the circulation. [Adapted from (25)].



evidence, a trial of intravenous L-carnitine (1 g intravenously after each dialysis session) might be considered reasonable in selected chronic dialysis patients with very large erythropoietin requirements who have undergone a complete negative examination for any reversible causes of anemia. Based on regimens used in controlled studies, therapy should be continued for perhaps 6 months, and response to therapy closely monitored.

Last but not least, L-carnitine affects the number and quality of erythrocytes in the circulation through multiple modes of action. Inhibition of apoptosis by L-carnitine is expected to increase red blood cells number. On the other hand, by promoting phospholipid remodelling and improving viscoelastic properties, L-carnitine is expected to affect erythrocytes quality, and hence, increasing their lifespan **(Figure 9)**[72].

A number of studies show that L-carnitine may favourably affect the impaired rheological properties of erythrocytes in hemodialysis patients. The salutary effects of L-carnitine on anemia center on improvement of erythrocyte survival, specifically through enhanced erythrocyte membrane stability[83,84]. In addition, antioxidant and anti-apoptotic effects of L-carnitine have also been described both *in vitro* in cultured endothelial cells and *ex vivo* in chronic hemodialysis patients[85-87] as well as by the improvement of inflammatory markers upon carnitine infusion[88,89].

Cardiovascular complications

Cardiovascular disease is the leading cause of mortality among patients with chronic kidney disease accounting for approximately half of all deaths in this patient population[90,91]. The high prevalence of cardiovascular diseases is attributable primarily to the large number and high prevalence of cardiovascular risk factors in these patients. Risk factors include both traditional risk factors such as diabetes and hypertension as well as unique non-traditional risk factors, including inflammation, oxidative stress, anemia, vascular calcification, and fluid and electrolyte shifts **(Table 2)**[91,92]. Manifestations of cardiovascular diseases in chronic kidney disease can be broadly classified as those affecting the myocardium and those affecting the blood vessels, although these pathophysiologic processes are not mutually exclusive and are in fact closely interrelated **(Figure 10)**. Clinical manifestations of myocardial and vascular remodelling include left ventricular hypertrophy, increased pulse pressure, and ischemic heart disease, all of which are independent risk factors for mortality in patients with kidney failure[91].

Cardiovascular alterations are partly reversible, and efforts should be directed toward early prevention with aggressive interventions on risk factors that lead to cardiovascular complications, adverse clinical events and death[90]. In this context, the antioxidant and anti-inflammatory properties of L-carnitine might be beneficial in uraemic patients[93].

Two placebo-controlled trials in hemodialysis patients independently demonstrated that intravenous L-carnitine reduced serum C-reactive protein and increased albumin, transferrin and body mass index[88,94]. In another double blind, randomized, controlled study, L-carnitine administration reduced serum amyloid A[95]. Chronically elevated levels of glucose and free fatty acids, as occur in type 2 diabetes, contribute to cell dysfunction by increasing the basal rate of insulin secretion, which can lead to insulin resistance. Because of its ability to regulate both lipid and glucose metabolism, L-carnitine administration ameliorated insulin resistance in dialysis patients[93,96]. The ability of L-carnitine to modulate several targets/pathways simultaneously might also justify a therapeutic use of this compound to reduce total cardiovascular risk in hypertensive subjects[93]. Moreover, in the study of Kazmi WH et al. patients with cardiovascular diseases, defined as hospitalizations for angina, myocardial infarction, arrhythmia, congestive heart failure, cerebral vascular disease or peripheral vascular disease prior to receiving L-carnitine, derived the greatest benefit from L-carnitine therapy. Administration of L-carnitine was associated with lower hospital utilization[97]. These results were supported by a follow-up analysis by Weinhandl et al. in a much larger US database containing data on over 116,000 hemodialysis patients. Treatment with L-carnitine resulted in a reduction of the future risk of hospital stay in the month following treatment, and this is even more remarkable after 1-month treatment[98]. Finally, as regards clinical manifestations of myocardial and vascular remodelling, it is well established that supplementation with L-carnitine induced regression of left ventricular hypertrophy in patients on hemodialysis[99]; a significant correlation between left ventricular ejection fraction and endogenous L-carnitine levels has also been reported, with patients exhibiting considerable improvement in the ejection fraction after administration of L-carnitine for 3 months[100]. Additional studies have provided similar findings[101-103].

Hypertriglyceridemia

Several heterogeneous studies evaluated the effect of L-carnitine supplementation on dialysis-related hypertriglyceridemia and revealed conflicting results. Only a few were randomized[36,47,67,77,104-106]. A recent systematic review that investigated the effect of L-carnitine supplementation in a total of 482 maintenance hemodialysis patients enrolled in 18 clinical trials failed to show an effect on triglycerides, total cholesterol, or any of its fractions[107].

Table 2. Manifestations of cardiovascular disease in chronic kidney disease and associated putative risk factors [Adapted from (91)].

Pathology	Traditional risk factors	Non-traditional risk factors
Cardiomyopathy	Older age Hypertension Valvular disease Dyslipidemia Smoking diabetes	Albuminuria Reduced glomerular filtration rate Anemia Inflammation Arteriosclerosis Extracellular fluid volume overload Abnormal calcium/phosphate metabolism
Atherosclerosis	Older age Male gender Hypertension Diabetes Dyslipidemia Smoking Physical inactivity Left ventricular hypertrophy	Albuminuria Reduced glomerular filtration rate Anemia Inflammation Oxidative stress Endothelial dysfunction Homocysteine Lipoprotein(a) Malnutrition Thrombogenic factors Sympathetic activity Insulin resistance/metabolic syndrome
Arteriosclerosis	Older age Male gender Smoking Hypertension Diabetes Dyslipidemia	Albuminuria Reduced glomerular filtration rate Endothelial dysfunction Abnormal calcium/phosphate metabolism Metabolic syndrome

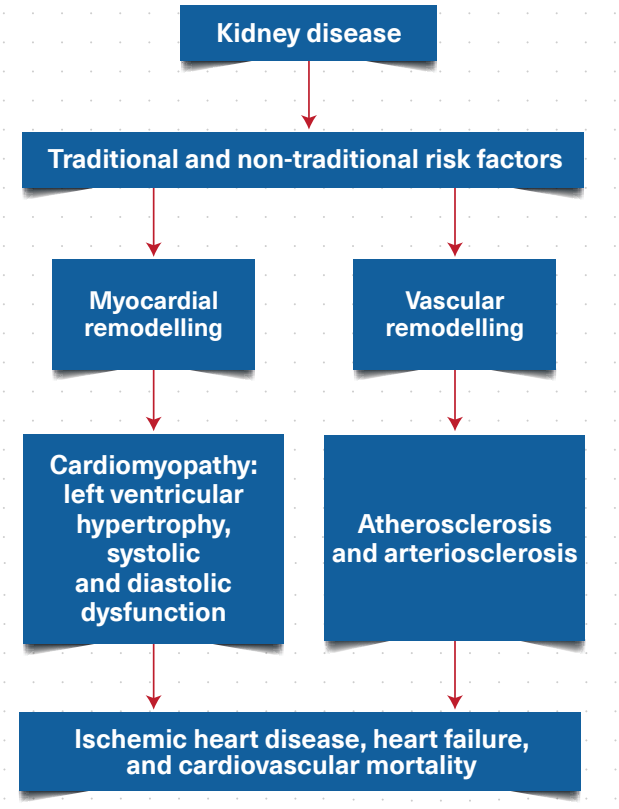


Figure 10. Traditional and non-traditional risk factors associated with chronic kidney disease may promote myocardial and blood vessel remodelling resulting in different manifestations of cardiovascular disease, including cardiomyopathy, atherosclerosis, and arteriosclerosis. [Adapted from (91)].

However, it is difficult to combine these studies in order to reach any meaningful conclusions regarding the use of L-carnitine, given that many were not randomized or controlled, enrolled small numbers of patients, and used variable doses, routes of administration, and durations of L-carnitine therapy. For example, although lower doses of L-carnitine (1-5 mg/kg intravenously administered at the end of each hemodialysis session) resulted in significant decreases in serum triglyceride levels in two small nonrandomized uncontrolled studies[108,109], larger doses of L-carnitine had no effect in a larger randomized controlled trial[104]. In a four-center, double-blind, placebo-controlled trial, 38 patients were randomized to receive up to 6 months of L-carnitine infusions (20 mg/kg) postdialysis and 44 patients were randomized to receive placebo infusions[104]. In both groups, baseline pre- and postdialysis plasma free carnitine levels were subnormal, predialysis plasma and red blood cell total carnitine levels were normal, and postdialysis total concentrations were subnormal. Although plasma and red blood cell total carnitine levels rose eightfold in the carnitine arm and remained unchanged in the placebo arm, there were no statistically significant changes observed in plasma triglycerides, high-density lipoproteins, or other lipoprotein parameters in either arm of the study[104].

Quality of Life

Studies also evaluated the effect of L-carnitine on quality of life or sense of well-being[110-112]. There was improvement in the sense of well-being after 2 months of therapy with 1-1.5 g intravenous L-carnitine in a randomized placebo-controlled study of 30 patients[110]. Brass et al.[111] used the validated self-administered Kidney Disease Questionnaire to assess quality of life at 12 and 24 weeks after intravenous L-carnitine therapy. There was a significant decrease from baseline in the fatigue component, but not in the other domains of the questionnaire. A study of 101 maintenance hemodialysis patients randomized subjects to either placebo or 1 g of L-carnitine orally immediately before and after every dialysis treatment for 6 months[112]. The Medical Outcomes Study Short Form 36 was used to assess health-related quality of life. Patients in the L-carnitine arm reported an early positive effect in general health ($p < 0.02$) and physical function ($p < 0.03$) that was not sustained throughout the 6 months of the study. What did correlate directly with perceived health-related quality of life was serum albumin concentration.

CONCLUSIONS

As chronic dialysis has become a more common therapy, health professionals have come to recognize a wide variety of metabolic abnormalities that accompany the uremic state and the state of dialysis dependence. A number of these abnormalities, including excess free radical production and inappropriate apoptosis, are affected by abnormalities in fatty-acid metabolism.

L-carnitine homeostasis, which is essential for fatty acid metabolism, is disrupted in ESRD patients on maintenance dialysis due to lower dietary intake, a decrease in endogenous renal synthesis, impaired fatty acid metabolism, and nonselective clearance by the dialysis procedure.

Moreover, as dialysis patients have serious morbidities that are multifactorial, individuals cannot be expected to respond in a uniform manner. Therefore, nephrologists might question the ethics of denying a benefit to a subset of patients merely because not all patients were similarly improved.

In light of the extensive evidence proving that:

- carnitine is an essential metabolic intermediate and carnitine deficiency can be a serious and life-threatening condition;
- hemodialysis depletes serum and, by extension, tissue carnitine stores;
- treatment of carnitine deficiency is efficacious as shown in data proving

that carnitine levels are maintained or even increased in patients under carnitine depletion and/or with low/falling carnitine levels, even if not explicitly in carnitine deficiency at the time of the study,

it would definitely be unethical to subject patients to the risks and discomforts of frank deficiency, to the point of maybe causing the onset of often irreversible complications, in order to prove a clinical benefit of carnitine supplementation.

Studies showed positive correlations between decreased L-carnitine levels and muscle weakness and anemia in patients on chronic dialysis. Clinical trials of L-carnitine supplementation to improve dialysis-related hypotension, muscle cramps, and heart failure revealed conflicting results. Most studies that showed subjective improvements in dialysis-related muscle symptoms, fatigue, and exercise capacity suffered from a lack of randomization and control groups, and a lack of standardized, validated measures of improvement in symptoms. There is some evidence to suggest that a trial of L-carnitine in anemic patients with large erythropoietin requirements may be beneficial. Underlying conditions for which a trial of L-carnitine is considered should be fully evaluated for reversible causes prior to consideration of L-carnitine supplementation. Whereas many of the clinical studies of levocarnitine in dialysis are limited by small patient numbers or problems with study design, there is surprising agreement among expert panels when evaluating the literature in aggregate.

In addition, as the cost of dialysis treatments continues to increase and patient outcomes continue to be less than desirable, dialysis providers must consider treating dialysis-related carnitine deficiency, given the strong evidence that its correction can lead to both an improvement in outcomes as well as a cost savings to the dialysis community. Some studies demonstrated association between carnitine therapy and lower hospital utilization among hemodialysis patients. Given the high cost associated with hospitalizations, the potential impact of carnitine therapy in dialysis patients deserves further investigation. An adequately powered randomized clinical trial that takes into account potential confounders could provide a final answer to this question. It could also help to solve existing controversies regarding the effects of carnitine and to identify potential subsets of patients who might benefit from this therapy.

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01

Prevalence of carnitine deficiency and decreased carnitine levels in patients on hemodialysis

Hatanaka Y, Higuchi T, Akiya Y, et al.

Blood Purif 2019; 47 Suppl 2:38-44

BACKGROUND AND AIM

- Patients on hemodialysis (HD) are known to develop carnitine deficiency. This deficiency may contribute to a number of clinical disorders, including cachexia, dyslipidemia, erythropoiesis stimulating agent-resistant anemia, insulin resistance and glucose intolerance, muscle weakness, and myopathy, as well as intradialytic symptoms, such as muscle cramps, hypotension, and cardiac arrhythmia.
- The aims of this study were to determine the prevalence of carnitine deficiency in Japanese patients undergoing dialysis and to compare the reduction rate of serum carnitine level between HD and on-line hemodiafiltration (HDF).

MATERIALS AND METHODS

- This research included an entire cohort population and a comparison study. All patients were treated with HD or HDF 3 times weekly in 4-5 h sessions. After exclusions, the final study population included 150 patients.
- Serum total, free, and acyl carnitine concentrations were measured, and the ratio of free carnitine to acylated carnitine was calculated. The prevalence of carnitine deficiency was then investigated.
- A free carnitine level < 20 μmol/L was defined as carnitine deficiency, a level in the range of 20-36 μmol/L as high risk of carnitine deficiency, and an acyl/free serum carnitine ratio > 0.4 as carnitine insufficiency, according to the Japanese guidelines.

RESULTS

- The mean serum total, free, and acyl carnitine levels were 40.0 ± 11.5, 25.4 ± 8.4, and 14.6 ± 4.7 μmol/L, respectively.
- The prevalence of carnitine deficiency and that of carnitine insufficiency was 25.3 and 86.7%, respectively. Patients at high risk of carnitine deficiency accounted for 64.7% (**Figure 1**). Only 10.0% of patients in the entire cohort had a normal free carnitine level. Multivariate regression identified an association of duration of dialysis with the free serum carnitine level. The reduction rates of serum free carnitine in HD and HDF were 64 ± 4 and 75 ± 7%, respectively ($p < 0.0001$) (**Figure 2**).
- Patients who were treated with levocarnitine were divided into an HD group and an HDF group. There was no significant difference in the pre-dialysis serum total, free, or acyl-carnitine concentration between the 2 groups. The reductions in serum total, free, and acyl carnitine were significantly higher in the HDF group.

key points

Carnitine deficiency is a clinical condition wherein the body is unable to use long-chain fatty acids in tissues as an energy source because the interstitial carnitine content is low.

In this study of patients on maintenance dialysis in Japan, the vast majority of patients had carnitine deficiency and were at high risk for carnitine deficiency.

Decreased serum carnitine levels were more common in patients on HDF than in those on HD.

FIGURE 1 **A** Histogram showing serum free carnitine concentrations in 150 patients on dialysis. **B** Histogram showing serum acyl/free carnitine concentration ratio in these patients.

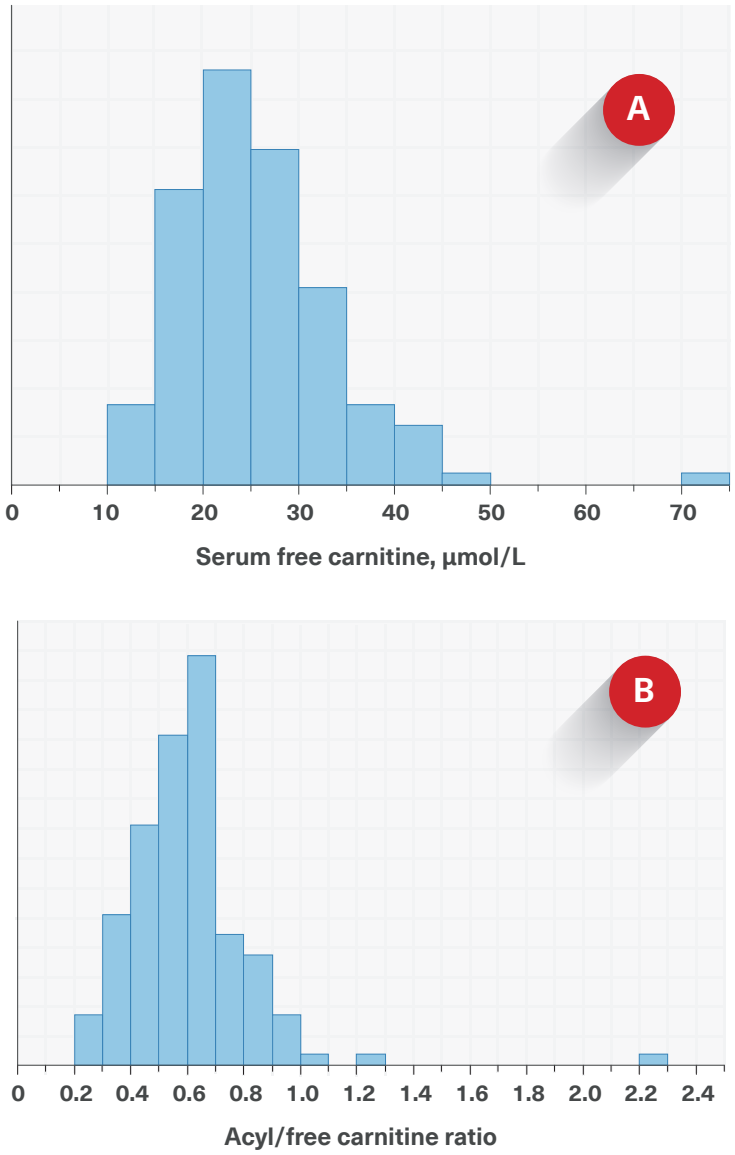
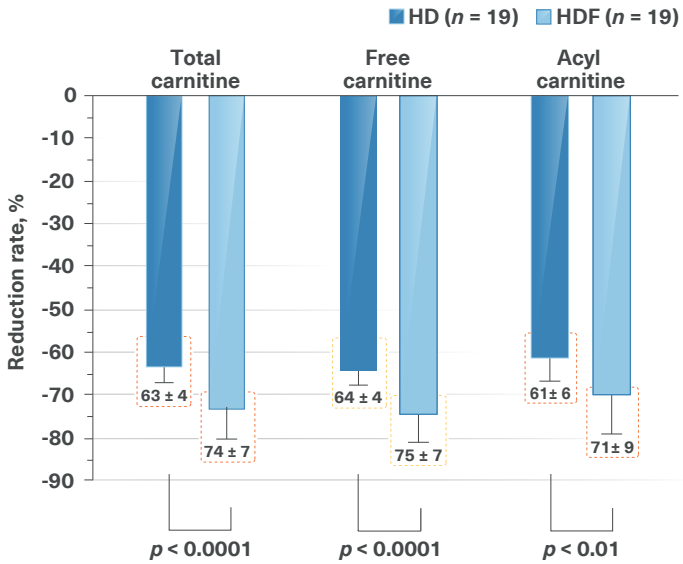


FIGURE 2 Reductions in serum total, free, and acyl carnitine concentrations in patients on HD or HDF. HD, hemodialysis; HDF, hemodiafiltration.



02

Carnitine in maintenance hemodialysis patients

Guarnieri G

J Ren Nutr 2015; 25(2):169-75

PHYSIOLOGICAL ROLE OF CARNITINE

- Carnitine is a conditionally essential metabolite that plays a critical role in cell physiology, since it is involved in many physiological functions such as: fatty acid transport to sites of β-oxidation in the mitochondria (**Figure**), where it also helps to prevent organic acid accumulation; storage and transport of energy between different organs; regulation of membrane phospholipids; osmolyte functions which might be relevant in the protection of cells and tissues from osmotic stress.
- Because of these key regulatory functions, carnitine represents a crucial determinant of mitochondrial energy metabolism, whose deficiency may lead to metabolic and clinical disturbances.

CARNITINE INSUFFICIENCY IN HEMODIALYSIS PATIENTS

- Patients on maintenance hemodialysis (MHD) treatment have low free carnitine plasma concentrations, with increased acylcarnitine-to-carnitine ratio, possibly because of preferential removal of free carnitine during dialysis sessions.
- Plasma levels of L-carnitine decline by approximately 60 to 70% during the course of a single dialysis session, and after 12 months of hemodialysis, endogenous plasma and muscle L-carnitine levels are approximately half of those measured before the initiation of hemodialysis treatment.
- Loss of carnitine through dialytic membranes occurs in maintenance hemodialysis, resulting in potential carnitine depletion and relative increments of esterified carnitine forms.
- Intradialytic loss of carnitine is not the only potential cause of carnitine depletion in hemodialysis patients as additional causes may include reduced carnitine intake or intestinal absorption as well as impaired carnitine de novo renal synthesis.

CARNITINE SUPPLEMENTATION TO HEMODIALYSIS PATIENTS

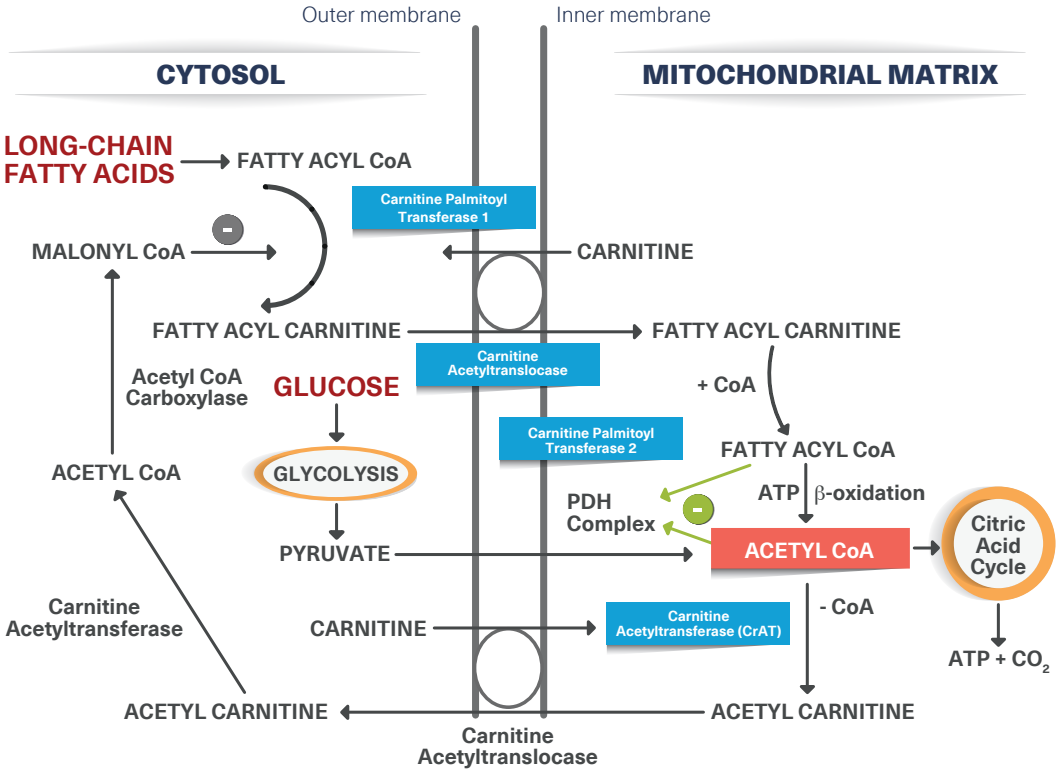
- Carnitine supplementation has been reported to counteract some of these alterations and has been associated with some clinical benefits in MHD patients, such as enhanced response to erythropoietin as well as improvement in exercise tolerance, intradialytic symptom, hyperparathyroidism, insulin resistance, inflammatory and oxidant status, protein-sparing effects, lipid profile, cardiac function, and quality of life.
- Furthermore, several studies reported in MHD patients supplemented with carnitine an improvement of anemia and of the response to erythropoietin (recombinant human EPO).
- At time, however, there are no definitive supportive studies and conclusive evidence that L-carnitine supplementation in maintenance hemodialysis patients could improve these conditions.

key points

Carnitine supplementation in MHD patients could be more beneficial for selected patient subgroups with more profound carnitine depletion such as older patients, female patients, and patients with longer disease duration.

A trial of carnitine administration could be attempted for 6 to 12 months only in selected patients on dialysis who do not adequately respond to standard therapies, in the presence of symptoms, in relation to how long the patient has been in dialysis and documented L-carnitine deficiency.

FIGURE Metabolic functions of carnitine. ATP, adenosine triphosphate; PDH, pyruvate dehydrogenase.



03

Association between 4-year all-cause mortality and carnitine profile in maintenance hemodialysis patients

Kamei Y, Kamei D, Tsuchiya K, et al.

PLoS One 2018; 13(8):e0201591

BACKGROUND AND AIM

- In hemodialysis patients, carnitine is constantly removed during the dialysis through dietary restrictions and decreased kidney function, which results in carnitine deficiency and reduced L-carnitine biosynthesis.
- Carnitine deficiency in hemodialysis patients can impair the efficiency of adenosine triphosphate (ATP) synthesis from long-chain fatty acids in the mitochondria. ATP is essential for life-sustaining activities, and a decrease in the efficiency of its synthesis may be related to disease prognosis and mortality.
- The aim of this study was to examine the relationship between β-oxidation efficiency represented by the carnitine profile and 4-year all-cause mortality in hemodialysis patients.

MATERIALS AND METHODS

- The study included 122 maintenance hemodialysis patients, whose carnitine profiles were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS).
- The associations between the 4-year all-cause mortality and carnitine profile as well as the clinical backgrounds of the patients were investigated.
- A survival analysis was conducted by the Kaplan-Meier survival method and multivariable Cox proportional hazard analysis.

RESULTS

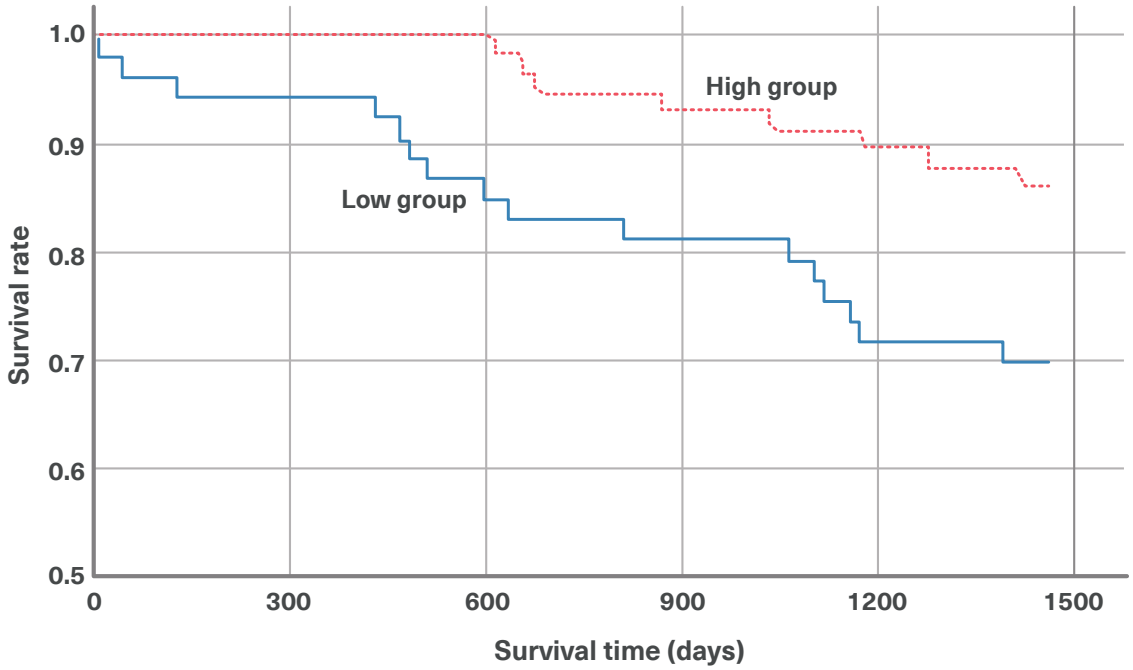
- Of the 122 subjects analyzed, 111 were selected and 24 died during the observation period.
- The diabetes state, age, and acetylcarnitine/(palmitoylcarnitine+octadecenoylcarnitine) [C2/(C16+C18:1)] level were determined to be significant prognostic factors. The diabetic state and age showed a positive correlation, while the C2/C16+C18:1 level showed a negative correlation to the survival rate.
- The patients were divided according to the median 41 of C2/(C16+C18:1) ratio into high group and low group and compared the survival rates between these groups. **Figure** shows the survival rates of these two groups as analyzed by Kaplan-Meier analysis, log-rank test, and Breslow test. The observation period was for 4 years, and the survival rates were 86.2% and 69.7% in the high and low groups, respectively. The survival rate was significantly higher in the high group than that in the low group (log-rank test; p = 0.027, Breslow test; p = 0.021).

key points

The present study revealed that 4-year all-cause mortality is positively correlated with the age and diabetes state and negatively correlated with the acetylcarnitine/(palmitoylcarnitine+octadecenoylcarnitine) [C2/(C16+C18:1)] ratio.

Improvement of the impaired β-oxidation state after L-carnitine administration may ameliorate prognosis.

FIGURE The survival probabilities of hemodialysis patients in high C2/(C16+C18:1) group or low C2/(C16+C18:1) group (log-rank test, P = 0.027. Breslow test, P = 0.021).



04

Association between resistance to erythropoiesis-stimulating agents and carnitine profile in patients on maintenance haemodialysis

Kamei D, Tsuchiya K, Nitta K, et al.

Nephrology (Carlton) 2018; 23(8):737-743

BACKGROUND AND AIM

- The majority of maintenance hemodialysis (MHD) patients have comorbid anemia, and anemia is known to exacerbate prognosis and decrease quality of life (QoL). In addition to decreased erythropoietin production in the kidney, it is considered that L-carnitine (LC) deficiency may be one important factor of this condition.
- The chronic carnitine-deficient state may be associated with abnormalities in fatty acid and organic acid metabolism.
- The aim of this study was to investigate the association between carnitine profiles before and after dialysis and the erythropoiesis-stimulating agent (ESA) resistance index (ERI), a significant prognostic factor in patients on maintenance hemodialysis.

MATERIALS AND METHODS

- In this cross-sectional study, the carnitine profile of 79 selected MHD patients was measured before and after dialysis using liquid chromatography-tandem mass spectrometry (LC-MS/MS).
- The ERI was defined as the average weekly dose of recombinant human erythropoietin (rHuEPO) over the prior 8 weeks (IU)/ post-dialysis body weight (kg) / hemoglobin (Hb) (g/dL). A darbepoetin α (DA): rHuEPO ratio of 200:1 was used for dose conversion of rHuEPO.
- The associations between the ERI and pre-dialysis carnitine profile, removal rate of various carnitines, and previously-reported ERI-related factors were investigated.
- Among the laboratory tests, the transferrin saturation (TSAT) was calculated using iron and total iron binding capacity (TIBC) measurements.

RESULTS

- **Table** shows the results of the univariate regression analysis between ERI and previously reported factors associated with ERI, pre-dialysis carnitine profile, and carnitine removal rate, and bootstrap results. In the present study population, TSAT was a factor that was significantly associated with ERI.
- Perhaps due to a narrow distribution of values, none of the other factors showed statistically significant associations.
- Regarding the pre-dialysis carnitine profile, 3-hydroxyisovalerylcarnitine (C5-OH) and glutarylcarnitine (C5DC) were significantly and negatively correlated with ERI, and stearoylcarnitine (C18) and octadecenoylcarnitine (C18:1) were significantly and positively correlated with ERI. Regarding the removal rate, none of the carnitine profiles demonstrated a significant association with ERI.

key points

The present study revealed that ERI is positively correlated with long-chain C18 acylcarnitine and is negatively correlated with short-chain C5-OH acylcarnitine.

C5-OH and C18 acylcarnitines at baseline might be contributing factors in distinguishing responders from nonresponders after L-carnitine administration.

TABLE The survival probabilities of hemodialysis patients in high C2/(C16+C18:1) group or low C2/(C16+C18:1) group (log-rank test, P = 0.027. Breslow test, P = 0.021).

			Bootstrap Result (2000 Replicas)				
	β	95%CI	*P*	Bias	S.E	95% CI	*P*
Age	-0.066	-0.148 to 0.081	0.561	0.000	0.048	-0.128 to 0.059	0.477
HD vintage	-0.062	-0.207 to 0.117	0.584	0.002	0.079	-0.204 to 0.106	0.574
diabetes states (yes = 1, no = 0)	-0.133	-6.784 to 1.733	0.241	-0.033	1.811	-6.072 to 1.097	0.166
ARB/ACEI Medication (yes = 1, no = 0)	-0.007	-3.473 to 3.273	0.953	0.049	1.679	-3.478 to 3.035	0.954
TSAT	-0.239	-33.031 to -1.377	0.034	0.025	8.623	-35.349 to -1.806	0.050
ferritin	-0.005	-0.027 to 0.026	0.962	-0.005	0.019	-0.043 to 0.026	0.972
sp Kt/Vun	0.030	-4.748 to 6.180	0.766	0.089	2.953	-4.678 to 7.024	0.811
β2MG	-0.074	-0.385 to 0.195	0.516	-0.004	0.195	-0.517 to 0.268	0.627
Alb	0.077	-3.166 to 6.444	0.499	0.173	2.167	-2.122 to 6.397	0.448
CRP	0.016	-2.155 to 2.491	0.886	0.189	1.221	-1.726 to 3.192	0.865
whole PTH	0.130	-0.007 to 0.025	0.255	0.000	0.015	-0.015 to 0.041	0.564
BSAP	0.083	-0.091 to 0.197	0.469	0.006	0.112	-0.134 to 0.312	0.620
C0	-0.10 3	-0.291 to 0.109	0.368	-0.019	0.114	-0.340 to 0.085	0.448
Acyl/C0	0.055	-7.409 to 12.205	0.628	0.362	4.000	-4.849 to 11.245	0.539
C2	0.022	-0.405 to 0.490	0.850	-0.029	0.207	-0.465 to 0.354	0.832
C3	-0.089	-14.808 to 6.422	0.434	-0.350	5.171	-15.647 to 4.872	0.424
C4	-0.216	-11.821 to 0.138	0.055	-0.030	3.094	-12.685 to -0.325	0.051
C5	0.021	-12.680 to 15.266	0.854	-4.353	11.254	-34.571 to 8.991	0.846
C5OH	-0.349	-87.038 to -21.072	0.002	0.151	18.004	-91.058 to -19.604	0.003
C5:1	-0.205	-165.901 to 6.580	0.070	0.002	46.492	-176.946 to 10.419	0.084
C5DC	-0.285	-8.705 to 1.173	0.011	0.006	2.254	-9.652 to -0.486	0.038
C6	-0.058	-56.635 to 33.667	0.614	5.527	30.944	-57.768 to 84.934	0.369
C8	-0.049	-8.003 to 5.159	0.668	1.787	5.543	-8.305 to 16.010	0.391
C10	-0.001	-4.679 to 4.625	0.991	1.620	3.627	-1.997 to 11.895	0.988
C10:1	-0.056	-12.853 to 7.765	0.625	0.229	4.684	-10.604 to 7.995	0.559
C12	0.081	-21.008 to 44.434	0.478	2.121	17.884	-15.596 to 57.116	0.479
C14	0.012	-128.505 to 142.540	0.918	2.667	74.219	-112.765 to 182.051	0.928
C14:1	0.069	-17.062 to 32.150	0.543	0.592	10.704	-11.490 to 30.364	0.468
C16	0.195	-7.321 to 108.785	0.086	-3.038	46.020	-31.347 to 141.768	0.325
C16 OH	0.116	-724.227 to 2261.525	0.308	-3.753	701.724	-594.879 to 2089.364	0.288
C18	0.244	14.362 to 275.538	0.030	-15.755	113.737	-65.220 to 349.228	0.260
C18:1OH	0.013	-646.842 to 723.910	0.911	19.852	284.987	-473.562 to 658.869	0.891
C18:1	0.231	1.402 to 63.069	0.041	-0.518	23.765	-7.038 to 83.570	0.193
C0 removal rate	-0.049	-24.795 to 15.982	0.668	-0.008	8.979	-22.783 to 13.072	0.624
C2 removal rate	0.005	-7.895 to 8.284	0.962	0.076	3.327	-5.790 to 7.225	0.956
C3 removal rate	0.082	-11.077 to 23.774	0.470	-1.115	7.855	-13.097 to 18.029	0.387
C4 removal rate	-0.078	-26.958 to 13.134	0.494	-0.221	10.369	-30.919 to 12.884	0.458
C5 removal rate	-0.104	-20.207 to 7.459	0.362	0.166	6.095	-17.986 to 5.606	0.319
C5OH removal rate	-0.053	-22.893 to 14.217	0.643	-0.379	8.257	-21.961 to 10.558	0.607
C5:1 removal rate	-0.059	-19.011 to 11.153	0.605	0.259	6.788	-16.221 to 9.879	0.571
C5DC removal rate	-0.198	-34.390 to 2.006	0.080	0.203	9.084	-33.762 to 2.739	0.077
C6 removal rate	0.051	-4.005 to 6.348	0.653	0.028	2.029	-2.621 to 5.377	0.565
C8 removal rate	0.152	-3.179 to 16.678	0.180	-0.026	4.834	-2.474 to 16.562	0.169
C10 removal rate	0.203	-0.633 to 14.285	0.072	0.202	3.294	0.794 to 13.829	0.035
C10:1 removal rate	0.167	-2.617 to 18.113	0.141	0.026	4.682	-1.307 to 17.122	0.104
C12 removal rate	0.087	-2.935 to 6.641	0.443	0.083	1.999	-1.871 to 6.184	0.336
C14 removal rate	-0.011	-5.135 to 4.646	0.921	0.047	1.958	-3.902 to 3.797	0.902
C14:1 removal rate	0.127	-0.627 to 2.251	0.265	0.018	0.638	-0.410 to 2.193	0.158
C16 removal rate	0.005	-6.733 to 7.058	0.963	0.087	3.221	-5.904 to 6.761	0.954
C16 OH removal rate	0.066	-4.882 to 8.917	0.562	0.009	2.901	-3.448 to 7.729	0.501
C18 removal rate	0.060	-7.004 to 12.067	0.599	0.122	4.457	-5.800 to 11.687	0.561
C18:1OH removal rate	0.029	-4.757 to 6.157	0.799	-0.065	2.061	-3.473 to 4.655	0.732
C18:1 removal rate	0.105	-1.832 to 5.029	0.356	-0.008	1.757	-1.633 to 5.337	0.359

Footnote: HD, hemodialysis; TSAT, transferrin saturation; β2MG, β2-macroglobulin; Alb, albumin; CRP, C-reactive protein; whole PTH, whole parathyroid hormone; BSAP, bone- specific alkaline phosphatase; C0, free carnitine; C2,Acetylcarnitine; C3, Propionylcarnitine; C4, Isobutyrylcarnitine; C5, Isovalerylcarnitine; C5-OH, 3-hydroxyisovalerylcarnitine; C5:1, Tiglylcarnitine; C5DC, Glutarylcarnitine; C6, Hexanoylcarnitine; C8, Octanoylcarnitine; C10, Decanoylcarnitin; C10:1, Decenoylcarnitine; C12, Dodecanoylcarnitine; C14, Tetradecanoylcarnitine; C14:1, Tetradecenoylcarnitine; C16, Palmitoylcarnitine; C16OH, 3-hydroxypalmitoylcarnitine; C18, stearoylcarnitine; C18:1-OH, 3-hydroxyoctadecenoylcarnitine; C18:1 Octadecenoylcarnitine.

05

L-carnitine improved the cardiac function via the effect on myocardial fatty acid metabolism in a hemodialysis patient

Kaneko M, Fukasawa H, Ishibuchi K, et al.

Intern Med 2018; 57(24):3593-3596

BACKGROUND AND AIM

- Patients undergoing maintenance hemodialysis (MHD) often have carnitine deficiency, which may contribute to clinical disorders, including erythropoiesis-stimulating agent (ESA)-resistant anemia, insulin resistance, endothelial dysfunction and muscle cramps. Furthermore, carnitine deficiency is known to cause cardiac dysfunction.
- L-carnitine administration may improve cardiac dysfunction [an increased left ventricular ejection fraction (LVEF) and a decreased left ventricular mass index (LVMI) and N-terminal pro brain natriuretic peptide (BNP)] in MHD patients.
- In this study is reported a case of dramatic improvement of cardiac dysfunction after L-carnitine administration. The Authors also investigated the myocardial fatty acid metabolism before and after the administration using ^{123}I-labeled β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP).

MATERIALS AND METHODS

- A 51-year-old woman had been suffering from sustained dyspnea [New York Heart Association (NYHA) functional classification, class III] for several months, with gradual enlargement of the cardiothoracic ratio (CTR, 72.3%) observed on chest X-ray.
- She had been on HD since 48 years of age due to end-stage renal disease (chronic glomerulonephritis suspected).
- Cardiac ultrasonography revealed mild to moderate hypokinesis of diffuse left ventricular wall motion without asynergy, a low LVEF, extreme left ventricular hypertrophy with increased LVMI
- The patient was started on treatment with intravenous L-carnitine at 2,000 mg/week (1,000 mg, twice a week) at the end of HD session.

RESULTS

- After several months, her symptom of dyspnea gradually improved.
- In addition, 1-year L-carnitine treatment increased her LVEF (from 50.6% to 71.2%) and decreased her LVMI (from 214.0 to 144.0 g/m^2) (**Table**).
- CTR (from 71.3% to 51.4%) and BNP concentrations (8,257 to 378 pg/mL) as well as the BMIPP summed scores [from 20 (severely impaired) to 6 (mildly impaired)] also improved (**Figure**).

key points

Carnitine deficiency in MHD patients is common as a result of the loss of carnitine during dialysis.

L-carnitine treatment can affect cardiac function via the improvement of abnormal myocardial fatty acid metabolism, suggesting that such treatment may be an option for MHHD patients with cardiac dysfunction of unknown cause.

FIGURE The clinical course before and after L-carnitine treatment. BMIPP: β-methyl-p-iodophenyl-pentadecanoic acid, BNP: brain natriuretic peptide, CTR: cardiothoracic ratio, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index

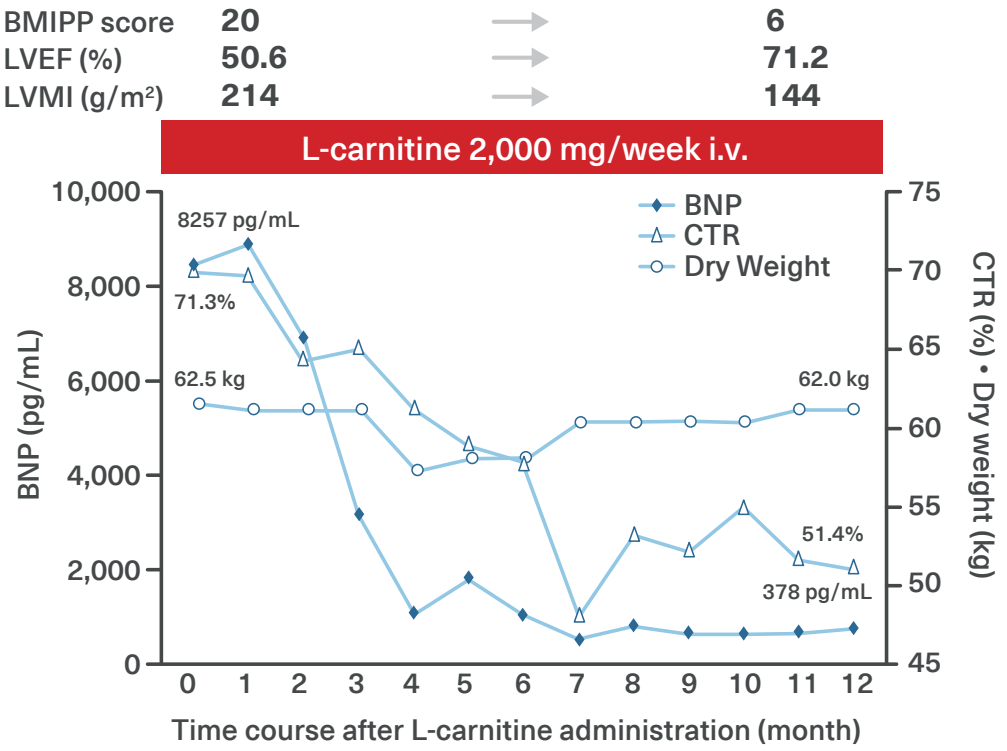


TABLE Findings of cardiac ultrasonography before and after L-carnitine treatment.

	L-carnitine treatment	
	Before	After
Left ventricular ejection fraction, %	50.6	71.2
Left ventricular dimension in diastole, mm	54.6	40.4
Left ventricular dimension in systole, mm	38.1	24.2
Interventricular septum thickness, mm	13.1	12.0
Left ventricular posterior wall thickness, mm	15.0	13.3
Left atrial dimension, mm	45.5	40.2
E/E' ratio	34.5	11.8
Left ventricular mass index, g/m²	214	144
Valvular diseases	MR II°, TR I°	None

06

Effects of intravenous L-carnitine on myocardial fatty acid imaging in hemodialysis patients: responders or non-responders to L-carnitine

Nishimura M, Tokoro T, Takatani T, et al.

Springerplus 2015;4:353

BACKGROUND AND AIM

- Carnitine plays an important role in myocardial fatty acid metabolism by transporting long-chain free fatty acids (FFA) from the cytoplasm to the matrix of myocardial and skeletal muscle mitochondria for β-oxidation.
- This study aimed to investigate whether chronic intravenous administration of L-carnitine could improve impaired myocardial fatty acid imaging in patients on maintenance hemodialysis with LV dysfunction not based on obstructive coronary artery disease (CAD) or valvular heart diseases.

MATERIALS AND METHODS

- The study enrolled 72 (40 men and 32 women, mean age: 64 ± 11 years; mean dialysis duration: 146 ± 96 months) hemodialysis (HD) patients who had impaired myocardial fatty acid imaging and left ventricular dysfunction, in absence of significant obstructive CAD identified by angiography.
- L-carnitine was intravenously administered for 1 year after each dialysis session to 36 participants (Carnitine group), while the other 36 participants were not administered L-carnitine (Control group).
- All participants underwent Coronary angiography (CAG), radionuclide imaging (resting 123I-BMIPP SPECT after fasting for over 6 h on a midweek, non-dialysis day within 1 month before the study and at 1 year after starting the study), echocardiography (on a midweek non-dialysis day within 1 month before the study, 6 months, and 12 months after starting the study), and biochemical and hematological determinations.

RESULTS

- During follow-up, 19 participants were discontinued from the study, and 53 participants (65 ± 12 years: 27 carnitine, 26 control) were analyzed.
- The mean BMIPP summed scores 1 year after carnitine administration did not differ from that before in the carnitine group, nor from that in the control group. However, improved SPECT (changes in BMIPP summed scores ≤ 20%) was found in 7 (25.9%) participants in the carnitine, whereas in 2 (7.7%) in the control group (**Figure**).
- Multivariate logistic analysis showed the improved SPECT was inversely associated with baseline serum albumin levels (1 g/L: odds ratio, 0.669); the cut-off was 35 g/L.

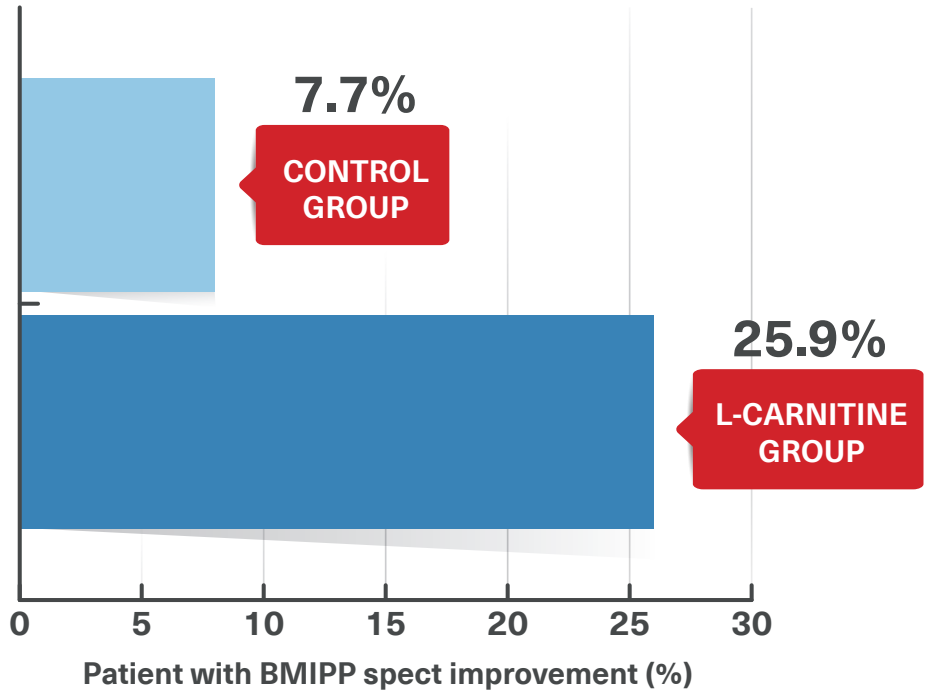
key points

L-carnitine did not improve myocardial fatty acid imaging evaluated by BMIPP SPECT in all hemodialysis patients with LV dysfunction.

However, L-carnitine might improve myocardial fatty acid imaging in a selected group of hemodialysis patients

With hypoalbuminemia (cut-off < 35 g/L), that could be considered one of the clinical parameters to select hemodialysis patients for administration of L-carnitine to improve fatty acid metabolism and cardiac dysfunction

FIGURE BMIPP SPECT summed scores before and 12 months after L-carnitine administration.



07

The unexpected effects of L-carnitine supplementation on lipid metabolism in hemodialysis patients

Katalinic L, Krtalic B, Jelakovic B, et al.

Kidney Blood Press Res 2018; 43(4):1113-1120

BACKGROUND AND AIM

- Dialysis-related carnitine deficiency (predialysis plasma concentration of free carnitine < 40 μmol/L) presents as the overlapping of anemia hyporesponsive to erythropoietin (EPO) therapy, intradialytic hypotension (IDH), cardiovascular (CV) complications and skeletal muscle dysfunction. However, results of L-carnitine supplementation in hemodialysis (HD) patients have been conflicting.
- With its major role as a metabolic intermediate, L-carnitine supplementation could improve nutritional status in HD patients.
- The main aim of this prospective study was to evaluate the effectiveness of intravenous L-carnitine in mitigating dialysis-related protein-energy wasting (PEW) based on pretreatment albumin levels.

MATERIALS AND METHODS

- This study enrolled 50 patients (46% male, mean age 63 ± 18.28 years, HD vintage 37.5 [7-288] months), based on the following inclusion criteria: at least 6 months of HD treatment, poor appetite with unintentional weight loss ≥ 5% over 3 months, and signs of PEW with serum albumin levels ≤ 38 g/L and Malnutrition-Inflammation Score (MIS) ≥ 5. Each patient received 1 g L-carnitine intravenously at the end of every HD session for 12 months.
- The evaluation comprised clinical data obtained from the medical records and charts, records of intradialytic hypotension periods (defined as a decrease of systolic blood pressure by ≥ 20 mmHg), and dietary habits evaluated using a self-administered questionnaire prior to L-carnitine supplementation. Laboratory parameters were measured prior to the supplementation and controlled in 6-months intervals.
- Anthropometric measurements were performed prior to HD session, and Malnutrition-inflammation score (MIS) was used as a scoring system representing the severity of PEW and an indicator of general functional capacity.

RESULTS

- L-carnitine supplementation had pronounced effects on lipid metabolism during the one-year period. Serum concentrations of HDL cholesterol decreased, while LDL cholesterol levels and fat tissue index (FTI) significantly increased. Although prealbumin fraction increased lean tissue index (LTI) fell, thereby leading to decreased LTI/FTI ratio (**Table**).
- When divided into two groups according to the pre-treatment albumin values (< 35 g/L or ≥ 35 g/L), patients from the higher albumin group showed significant increase in prealbumin (p=0.005), and improved MIS (p = 0.03).
- Higher FTI after introduction of L-carnitine led to greater hemodynamic stability (OR 1.709, 95% CI 1.006-2.905, p = 0.048).

key points

L-carnitine supplementation showed significant effect on lipid metabolism and nutritional status, although further clinical trials and experimental research are needed to define the role of lipid metabolism in CKD population.

Significant benefits of L-carnitine supplementation in patients with better initial serum albumin levels suggest that this therapy should not be restricted to patients with the worst nutritional and overall status.

TABLE Parameters in both groups according to albumin values prior and after L-carnitine supplementation. *Wilcoxon test

Parameter	Serum albumin < 35 g/L median (interquartile range)		P*	Serum albumin ≥ 35 g/L median (interquartile range)		P*
	Prior (N = 12)	After (N = 11)		Prior (N = 37)	After (N = 33)	
Body weight (kg)	70.5 (59-81.83)	74 (55-89)	0.201	67 (44-112)	67 (44-112)	0.456
Body height (cm)	171 (159-181)	168 (164-181)	0.500	167 (153-160)	168 (153-179)	0.366
BMI (kg/m²)	24.5 (20.68-30)	26.1 (21.86-33.09)	0.513	24.35 (17.1-35)	24.84 (16.85-33.81)	0.931
Cholesterol (mmol/L)	3.65 (3.15-4.68)	3.4 (2.8-5.1)	0.648	4 (2.2-7.8)	4.1 (2.6-8.4)	0.049
Triglycerides (mmol/L)	0.89 (0.08-5.13)	1.12 (0.1-3.05)	0.112	1.25 (0.52-35.13)	1.47 (0.29-26.14)	0.226
HDL (mmol/L)	1.17 (0.22-1.88)	1.08 (0.67-2.08)	0.495	1.07 (0.68-2.13)	0.92 (0.6-1.9)	0.002
LDL (mmol/L)	1.79 (0.89-3.65)	1.87 (0.44-3.56)	0.280	2.32 (0.81-5.14)	2.54 (1.65-5.38)	0.007
Hemoglobin (g/L)	109 (92.5-118.25)	113 (104-119)	0.158	111 (85-150)	108 (91-147)	0.627
Ferritin (µg/L)	190.25 (19.9-833.1)	210.6 (67.7-1025)	0.009	359 (37.5-1141)	412.1 (35.2-1034)	0.133
Iron (µmol/L)	14.5 (7-25)	10 (3-18)	0.139	11 (5-33)	14 (5-27)	0.329
EPO dose (IU/month)	32000 (8000-48000)	48000 (16000-48000)	0.99	32000 (0-72000)	24000 (0-64000)	0.596
IV Fe dose (mg/month)	125 (0-250)	125 (0-250)	0.102	125 (0-400)	122 (0-250)	0.027
Potassium (mmol/L)	4.3 (3.5-5.7)	4.9 (3.8-6.2)	0.055	5.1 (4.3-7.2)	5.3 (3.8-6.4)	0.637
Calcium (mmol/L)	2.33 (2.17-2.52)	2.28 (2.02-2.48)	0.198	2.24 (1.95-2.71)	2.26 (1.9-2.7)	0.467
Phosphorus (mmol/L)	1.41 (0.72-2.13)	1.33 (0.36-2.25)	0.363	1.68 (0.74-3.07)	1.82 (0.87-3.32)	0.047
Total protein (g/L)	63 (51-69)	60 (45-75)	0.875	66 (56-77)	67 (60-75)	0.105
Serum albumin (g/L)	34.25 (31-35)	33.2 (26.1-34.8)	0.280	37.6 (35.2-44.2)	38.7 (35.3-44.3)	0.338
MIS	11.5 (6-16)	11 (8-18)	0.899	8 (5-13)	6 (2-15)	0.030
Prealbumin (g/L)	0.45 (0.3-0.7)	0.5 (0.4-1.7)	0.055	0.6 (0.4-0.8)	0.7 (0.4-0.9)	0.005
Overhydration (L)	2.05 (-0.7-6.8)	2.1 (0.1-5.1)	0.753	2.2 (-2.1-6.8)	2.1 (-9-5.2)	0.532
LTI (kg/m²)	11.1 (6.6-15.6)	9.5 (5.8-14.4)	0.140	12.9 (8.8-21.1)	11.25 (6.4-15.3)	0.004
FTI (kg/m²)	12.15 (0.5-24)	16.3 (2.7-26.2)	0.293	10.65 (4.7-23.3)	13 (4.1-21.4)	0.001
LTI/FTI ratio	0.93 (0.29-28.6)	0.55 (0.22-4.52)	0.088	1.27 (0.38-3.26)	0.98 (0.34-3.32)	0.005

08

Effects of L-carnitine on mineral metabolism in the multicentre, randomized, double blind, placebo-controlled CARNIDIAL trial

Mercadal L, Tezenas du Montcel S, Chonchol MB, et al.

Am J Nephrol 2018; 48(5):349-356

BACKGROUND AND AIM

- A favourable effect of L-carnitine treatment on bone mineralization in osteoporotic men and on phosphate levels in HD patients has been previously reported. In these studies, the effects of L-carnitine treatment on the circulating levels of the hormones controlling plasma calcium and phosphate have not been examined.
- The aim of this study was to evaluate the effects of L-carnitine supplementation on parameters of chronic kidney disease-mineral bone disorder.

MATERIALS AND METHODS

- The CARNIDIAL study enrolled 92 HD subjects who have been on dialysis for less than 6 months, randomized to receive 1 year of L-carnitine 1 g intravenously (n = 46) at the end of each dialysis session versus placebo (n = 46) in double blind.
- The L-carnitine effect on mineral metabolism was analyzed by determinant factors of C-terminal fibroblast growth factor 23 (cFGF23) and intact FGF23, including Klotho level.
- FGF23 is a hormone produced by osteocytes and osteoblasts that control phosphate and vitamin D metabolism, and its plasma concentration is markedly increased with declining kidney function and strongly related to a higher risk of death. FGF23 physiologic effects require the presence of its co-receptor αKlotho, a protein whose expression is restricted to a few organs including the kidney.

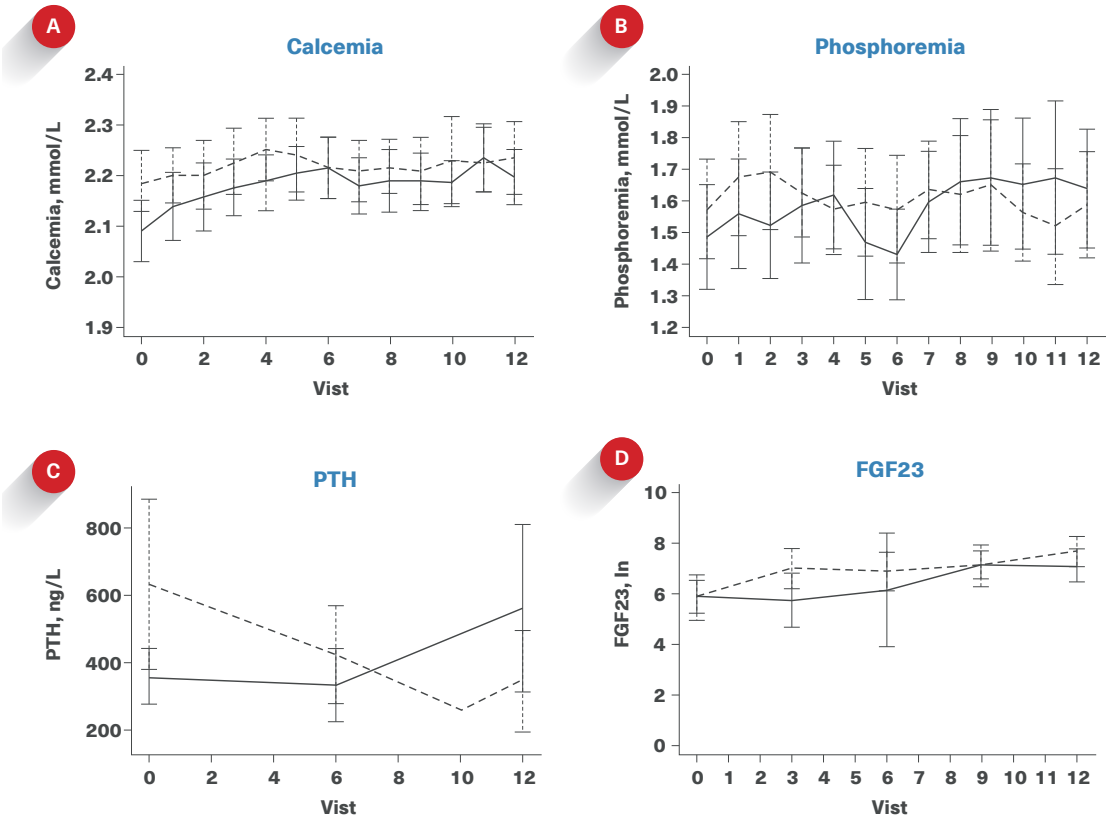
RESULTS

- The cFGF23 concentration was positively correlated to calcium, phosphate and Hb levels, and negatively correlated to PTH, ESA dose and ESA resistance index. No correlation was found between cFGF23 and iron markers or weekly and 12-months cumulative iron dose.
- Klotho was below the lower limit of quantification (LLOQ) in 55% of the 163 samples. In multivariate analysis, cFGF23 was positively correlated with calcium and phosphate and was higher in subjects having Klotho > LLOQ. No correlation existed between Klotho and phosphate and phosphate was even higher in subjects having Klotho > LLOQ ($p < 0.001$).
- Both forms of FGF23 were not related to iron markers nor to IV iron dose.
- Calcium, lower at inclusion in the L-carnitine group, increased significantly more during the 1 year period in this group (**Figure**). Phosphate also increased more in the L-carnitine group. PTH and FGF23 had a similar course in the 2 treatment groups where PTH slightly decreased over time, whereas FGF23 increased.

key points

L-carnitine supplementation increased calcium and phosphate plasma concentrations with no detected down-regulation effect on PTH and FGF23.

FIGURE Plasma Calcium (**A**), phosphate (b), PTH (**C**) and FGF23 (**D**) course during the 1 year study period according to treatment arm. Solid line carnitine group, dotted line placebo group. PTH, parathyroid hormone; FGF23, fibroblast growth factor 23.



09

Efficacy of L-carnitine supplementation for improving lean body mass and physical function in patients on hemodialysis: a randomized controlled trial

Maruyama T, Maruyama N, Higuchi T, et al.

Eur J Clin Nutr 2019; 73(2):293-301

BACKGROUND AND AIM

- Sarcopenia is common in patients with chronic kidney disease and is associated with adverse clinical outcomes, especially in individuals with end-stage kidney disease (ESKD) on maintenance hemodialysis (HD). In spite of the clinical significance of sarcopenia, there are but a few comprehensive intervention programs. Amino acid deficiency, including carnitine deficiency, is thought to be associated with the pathophysiology of this syndrome. However, the effects of L-carnitine on physical function in patients on HD have not been documented.
- The aim of this study was to determine the effects of L-carnitine treatment for 12 months on the physical and nutritional status of patients undergoing HD.

MATERIALS AND METHODS

- In this multicenter, prospective, parallel, randomized, controlled trial, 91 patients on hemodialysis who developed carnitine deficiency were randomly assigned to receive injections of 1,000 mg L-carnitine 3 times per week after each hemodialysis session (L-carnitine group, n = 45) or no injections (control group, n = 46) with monitoring for 12 months. The data for 84 of the 91 patients were available for analysis (L-carnitine group, n = 42; control group, n = 42).
- The inclusion criteria were as follows: age ≥ 20 years and ≤ 85 years, duration of HD > 12 months at enrollment, carnitine deficiency (free plasma carnitine concentration < 40 μmol/L), and patients for whom medical decisions were made at the participating hospitals.
- All eligible participants were required to undergo dual-energy X-ray absorptiometry (DXA) scans to determine their lean body mass (LBM), fat mass, and skeletal muscle mass.

RESULTS

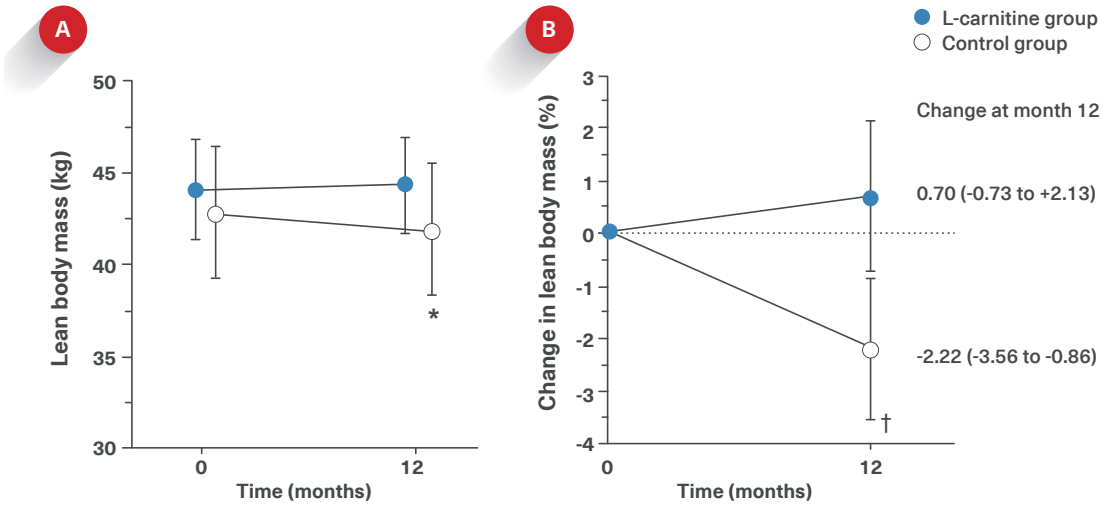
- There was no significant change in dry weight in the L-carnitine group (from 57.4 ± 10.9 kg at baseline to 57.7 ± 11.1 kg at the end of the study; P = 0.419); however, there was a significant decrease in dry weight in the control group (from 58.4 ± 12.2 kg to 57.8 ± 12.9 kg; P = 0.035). The difference in the mean change in dry weight in the L-carnitine group versus the control group at the end of the study was 1.95% (95% CI: -0.36, -0.02; p = 0.021).
- There was no significant change in BMI in the L-carnitine group, but BMI decreased significantly from 21.5 ± 3.8 at baseline to 21.2 ± 3.9 at the end of the study in the control group (p = 0.044). The difference in the mean change in BMI in the L-carnitine group versus the control group by the end of the study was 2.18% (95% CI: -0.51, -0.07; p =0.004).
- There was no significant change in LBM in the L-carnitine group (44.6 ± 7.5 kg at baseline, 44.9 ± 7.3 kg at 12 months; p = 0.224) (**Figure**); however, there was a significant decrease in LBM in the control group (from 43.3 ± 9.8 kg at baseline to 42.5 ± 9.7 kg at 12 months; p = 0.009). The difference in the mean change in LBM between the groups at 12 months was 2.92 % (95% CI: 1.28-4.61; p = 0.0007).

key points

L-carnitine injection is useful for prevention of muscle weakness in patients who develop carnitine deficiency while on HD.

The benefits of L-carnitine supplementation in these patients include maintenance of both physical function and LBM.

FIGURE Changes in arm muscle area (AMA) in the L-carnitine and control groups. **A** AMA. **B** Percent change in mean AMA. The data are shown as the mean and 95% confidence interval. Cohen's d = 0.69. *P < 0.01 *vs* baseline. †P < 0.01 *vs* L-carnitine group.



10

Carnitine therapy is associated with decreased hospital utilization among hemodialysis patients

Kazmi WH, Obrador GT, Sternberg M, et al.

Am J Nephrol 2005; 25(2):106-15

BACKGROUND AND AIM

- Hospitalizations account for 41% of the end-stage renal disease (ESRD) cost, and hence, are a prime target for reduction in resource utilization and cost containment.
- Carnitine deficiency is common among chronic hemodialysis patients, and its correction is related to improvements in anemia, and cardiac and skeletal muscle function.
- In view of the potential improvements in cardiac function and anemia, this study evaluated the potential effect of carnitine therapy in reducing hospitalization rates among chronic hemodialysis patients.

MATERIALS AND METHODS

- This was a retrospective analysis of data obtained from Fresenius Medical Care (FMC) North America. A total of 2,990 adult patients who received carnitine for at least 3 months, and had at least 3 months of pre-carnitine follow-up, were included in the analysis.
- The cause of ESRD was hypertension in 40%, diabetes in 37%, glomerular disease in 8%, and other causes in 15%. The mean follow-up during the pre-carnitine period was 10.5 ± 2.6 months (max 12 months, min 3 months). The average duration of carnitine use was 9.7 ± 5.4 months, which was also the average follow-up period during carnitine treatment.

RESULTS

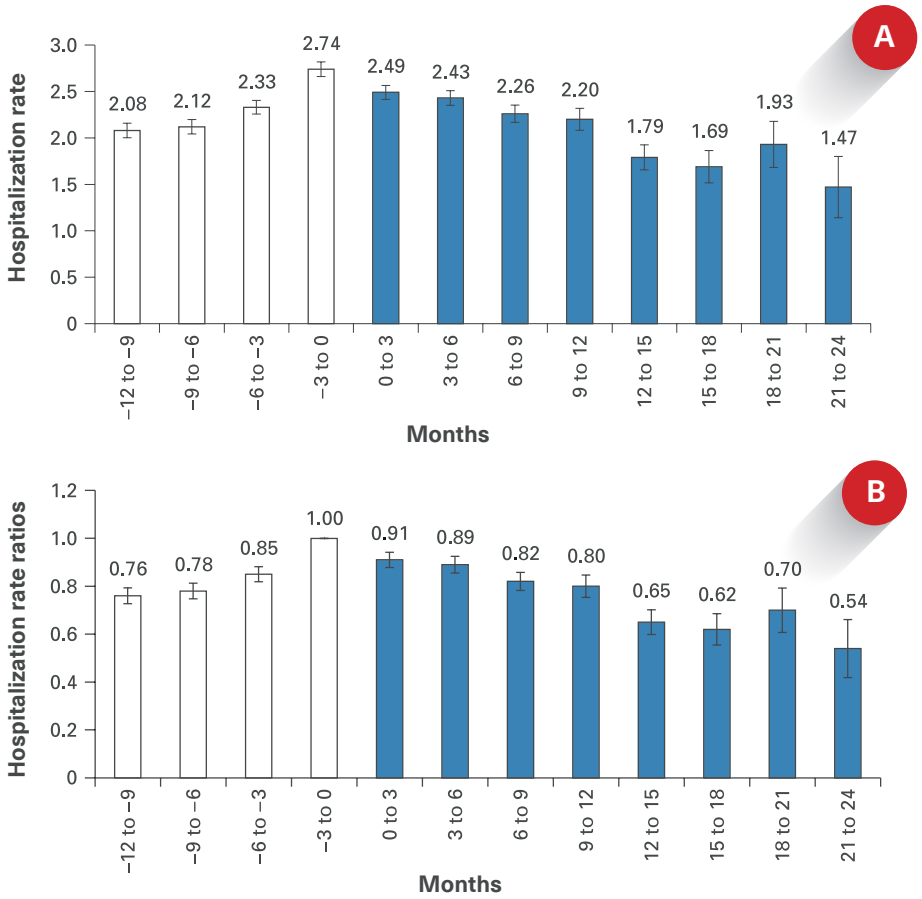
- Carnitine therapy (at a mean dose of 1.5 ± 0.7 g per administration) was associated with a significant reduction in hospital utilization. During the carnitine period, the unadjusted rates of hospitalization per patient-year at risk decreased to 2.49 at 0-3 months and to 2.43 at 3-6 months and continued to decrease thereafter (**Figure, panel A**). Compared to the hospitalization rate at -3 to 0 months in the pre- carnitine period, the hospitalization rate ratios during the carnitine period decreased to 0.91 at 0-3 months, 0.89 at 3-6 months and to 0.80 at 9-12 months (**Figure, panel B**).
- The greatest benefit from carnitine therapy was observed in patients with cardiovascular disease (defined as hospitalizations for angina, myocardial infarction, arrhythmia, congestive heart failure, cerebral vascular disease or peripheral vascular disease prior to receiving carnitine), and those with anemia and hypoalbuminemia.
- Compared to 3 months prior to the initiation of carnitine, the adjusted relative risk for hospitalization was 11, 11, and 15% lower at 3, 6, and 9 months, respectively. Among patients with cardiovascular disease, the reduction in risk was even more significant (24, 31, and 34% lower at 3, 6, and 9 months, respectively).

key points

This study demonstrates association between carnitine therapy and lower hospital utilization among hemodialysis patients.

Patients with cardiovascular disease, anemia, and hypoalbuminemia derived the greatest benefit from carnitine therapy.

FIGURE Unadjusted rates (**A**) and rate ratios (**B**) of hospitalization per patient-year at risk before and during treatment with L-carnitine. *White columns*: before carnitine, *blue columns*: during carnitine.



11

Protective effect of intravenous levocarnitine on subsequent-month hospitalization among prevalent hemodialysis patients, 1998 to 2003

Weinhandl ED, Rao M, Gilbertson DT, et al.

Am J Kidney Dis 2007; 50(5):803-12

BACKGROUND AND AIM

- Approximately 75% of free L-carnitine was removed from plasma during each hemodialysis session, resulting in a continual decrease from prehemodialysis levels, and as many as 95% of hemodialysis patients experience dialysis-related carnitine deficiency.
- Intravenous L-carnitine therapy for patients with end-stage renal disease (ESRD) may be efficacious, but evidence in support of its use is conflicting.
- This study used data of Centers for Medicare & Medicaid Services (CMS) to analyze the effect of intravenous L-carnitine therapy on subsequent hospitalization days in prevalent hemodialysis patients between 1998 (when levocarnitine was approved for use in patients with ESRD) and 2003.

MATERIALS AND METHODS

- A retrospective analysis of the effect of intravenous levocarnitine therapy on prevalent hemodialysis patients with Medicare as primary payer for health care services was performed. Hospitalization days was calculated from Medicare inpatient claims.
- Sample sizes of the 6 cohorts studied increased with time, from a minimum of 116,534 in 1998 to a maximum of 153,081 in 2003. The percentage of patients receiving any L-carnitine during follow-up increased from a low of 3.8% in 1998 to a peak of 7.2% in 2000, decreasing to 4.6% in 2003.
- Outcome and measurements included the effect of 1 g or greater per dialysis session of L-carnitine for 10 or more sessions during a month on subsequent hospitalization days. Repeated-measures and marginal structural models were fit, the latter to account for time-dependent confounding.

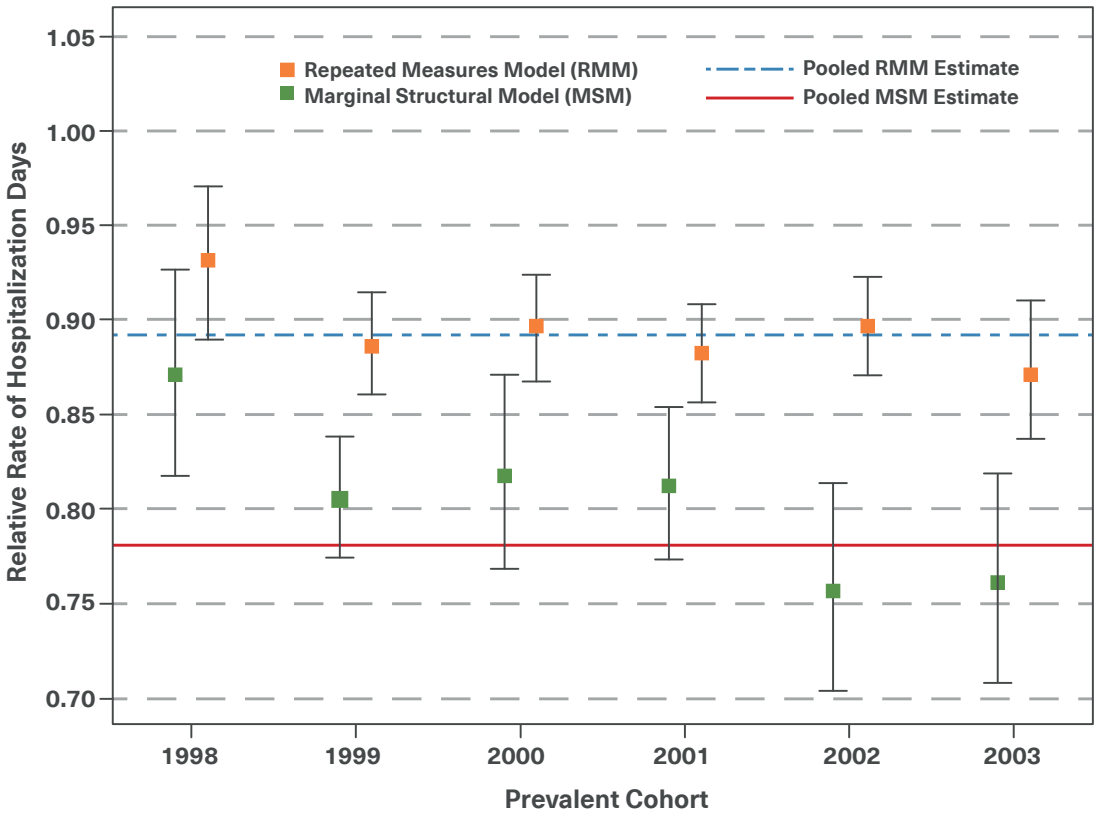
RESULTS

- Of the study population, 3% to 7% received levocarnitine for 1 month per year or more. Treated patients were older with more severe comorbidity and larger erythropoietin doses than untreated patients.
- In repeated-measures model analysis adjusted for demographic characteristics and disease severity, 1 g or greater per dialysis session of levocarnitine for 10 or more sessions during a month was associated with a 10.8% (95% confidence interval, 9.7 to 11.9; $p < 0.01$) subsequent-month decrease in hospitalization days (**Figure**).
- In marginal structural model analysis, L-carnitine therapy was associated with a 21.7% (95% confidence interval, 18.4 to 24.9; $p < 0.01$) decrease in hospitalization days.
- Of note, older age and longer ESRD vintage, diabetes as a primary cause of ESRD, and increased EPO dosage and a history of hospitalization during the entry period were all significantly associated with increased hospitalization rates.

key points

Because hemodialysis patients are hospitalized about 15 days yearly, the association of monthly levocarnitine regimen with lower hospitalization rate is clinically significant.

FIGURE In the repeated-measures model, administration of 1 g/s or greater of L-carnitine for 10 or more sessions during a month was significantly associated with a decrease in hospitalization days during the subsequent month for each prevalent cohort.



12

Inflammation and L-carnitine therapy in hemodialysis patients: a review

Khalatbari-Soltani S, Tabibi H

Clin Exp Nephrol 2015, 19(3):331-335

INFLAMMATION IN HEMODIALYSIS PATIENTS

- Inflammation is a common complication in hemodialysis (HD) which is found in 30-50% of the patients, and can result in some complications, especially cardiovascular diseases, protein-energy wasting and erythropoietin-resistant anemia.
- In HD patients, chronic inflammation may result from the repeated contact of blood mononuclear cells with dialysis tubes and dialyzer membranes, impurities in the dialysis water and/or dialysis solution, oxidative and carbonyl stress, increased release and decreased clearance of inflammatory cytokines.
- In addition, carnitine deficiency occurs frequently in HD patients because of impaired de novo carnitine renal synthesis and reduced dietary intake.

CARNITINE METABOLISM IN HD PATIENTS

- Carnitine deficiency is prevalent in HD patients, and can result clinically in muscle weakness, muscle cramps, myopathy, cardiomyopathy, and cardiac arrhythmia, loss of body protein, cachexia, insulin resistance, altered plasma lipid profile, and erythropoietin-resistant anemia.
- Carnitine deficiency in HD patients is characterized by a reduction in plasma free L-carnitine concentration and tissue L-carnitine stores and an increase in the ratio of acylcarnitine to free L-carnitine.

TRIALS ON THE EFFECTS OF L-CARNITINE ON INFLAMMATION IN HD PATIENTS

- According to available literature, only 8 trials have investigated the effects of L-carnitine supplement on inflammatory markers.
- In the majority of these studies, L-carnitine supplementation, both orally and intravenously, was associated to a significant reduction of serum C-reactive protein (CRP) and amyloid A (SAA) levels. Serum CRP is a strong predictor of mortality, especially cardiovascular mortality in HD patients, whereas elevated SAA concentration is a risk factor of cardiovascular diseases.
- Furthermore, in one study was hypothesized that the decrease of serum CRP and SAA by administration of L-carnitine may be possibly due to reducing serum IL-6 also.

RECOMMENDED DOSE AND ROUTE FOR L-CARNITINE THERAPY

- According to the literature, intravenous L-carnitine should be administered at a dose of 20 mg/kg or 1,000 mg/day thrice weekly at the end of each hemodialysis session for reducing inflammation, whereas oral L-carnitine at a dose of 1,000 mg/day can reduce inflammation in HD patients.
- Some studies indicated that high serum trimethylamine-N-oxide was associated with cardiovascular diseases and one atherosclerotic mechanism observed for trimethylamine-N-oxide is reduction of reverse cholesterol transport. For this reason, oral L-carnitine is not recommended and the intravenous route is the best way for carnitine therapy in HD patients with inflammation (hs-CRP > 3 mg/L).

key points

All studies on the effects of L-carnitine supplementation on systemic inflammation, except one, showed that L-carnitine could significantly reduce serum CRP and SAA, as two systemic inflammation markers, in HD patients.

Considering the high prevalence of inflammation and carnitine deficiency in HD patients, L-carnitine therapy is a reasonable approach for reducing systemic inflammation and its complications in these patients.

13

Supplementation with high-dose L-carnitine on hemodialysis tolerance in uremic patients with severe heart disease

Pan YJ, Lu FP

Zhonghua Yi Xue Za Zhi 2017; 97(48):3792-3795

AIM

- To investigate the effect of intravenous supplementation with high-dose L-carnitine on hemodialysis tolerance in uremic patients with severe heart disease (ischemic heart disease, congestive heart disease and arrhythmia).

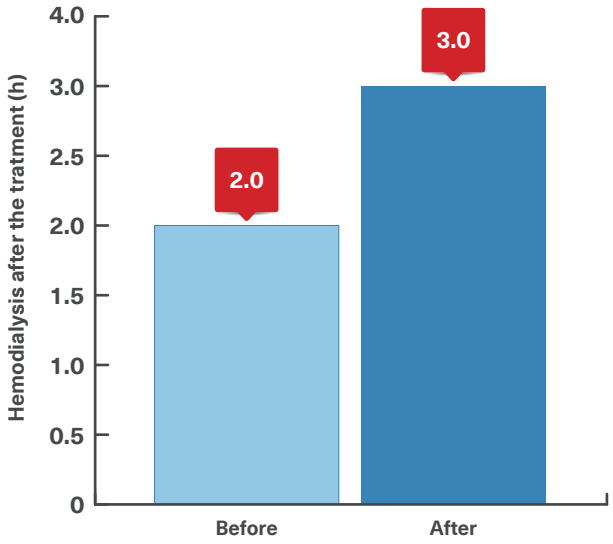
MATERIALS AND METHODS

- Between March 2012 and March 2017, L-carnitine 5,000 mg was given after the completion of each hemodialysis treatment (3-4 times a week) over a period of two weeks in 29 maintenance hemodialysis patients with severe heart diseases manifested by frequently symptomatic hypotension, chest tightness, wheezing, palpitation, chest pain and other symptoms during hemodialysis.
- The hemodialysis duration, heart functional classification (New York Heart Association Functional Classification, NYHA), blood pressure and arrhythmia were analyzed before and after the treatment.

RESULTS

- The duration of hemodialysis was significantly prolonged after treatment [from 2.0-3.5 (2.6 ± 0.4) h to 3.0-4.0 (3.8 ± 0.4) h, t = 10.66, p < 0.01] (**Figure**).
- Cardiac function was improved (Z = -4.74, P < 0.01). The hypotension and arrhythmia during dialysis was improved.

FIGURE Duration of hemodialysis before and after treatment with L-carnitine.



key points

High-dose of intravenous L-carnitine supplementation can improve hemodialysis tolerance and the symptoms of heart failure, arrhythmia, ischemic cardiac disease in hemodialysis patients with severe heart diseases.

14

Kinetics of carnitine concentration after switching from oral administration to intravenous injection in hemodialysis patients

Suzuki A, Sakai Y, Hashimoto K, et al.

Ren Fail 2018; 40(1):196-200

BACKGROUND AND AIM

- Carnitine has high dialyzability and is often deficient in hemodialysis (HD) patients, because these patients are undernourished due to inflammation.
- Carnitine is used for treating carnitine deficiency, either by IV or oral supplementation. In HD patients, particularly, IV administration is often provided after dialysis. However, there are no reports available on the appropriate carnitine doses, administration methods, and dosing period for HD patients.
- This study aimed to evaluate kinetics of carnitine when the mode of administration was changed from oral to IV in the same HD patient.

MATERIALS AND METHODS

- This was a single-center, one-way, open-labeled, prospective study, in which 17 stable-maintenance HD patients treated by oral dosing of L-carnitine (200 mg, thrice a day (n = 5) or 300 mg, thrice a day (n = 12)] for at least 11 months were enrolled (12 men and 5 women; age: 61.6 ± 9.2; time on HD 8.3 ± 6.2 years), were switched to an IV dosing mode (1,000 mg/day, after every dialysis).
- Carnitine kinetics were evaluated by plasma sampling at 0 and 2 weeks, 3, 6 and 12 months of switching to the IV dosing and at 3, 6, 9 and 12 months after terminating the dosing.
- The carnitine kinetics were also evaluated by determining the plasma concentrations of total carnitine (TC), acyl-carnitine (AC), free-carnitine (FC), and the AC/FC ratio, which evaluates the relative lack of FC.

RESULTS

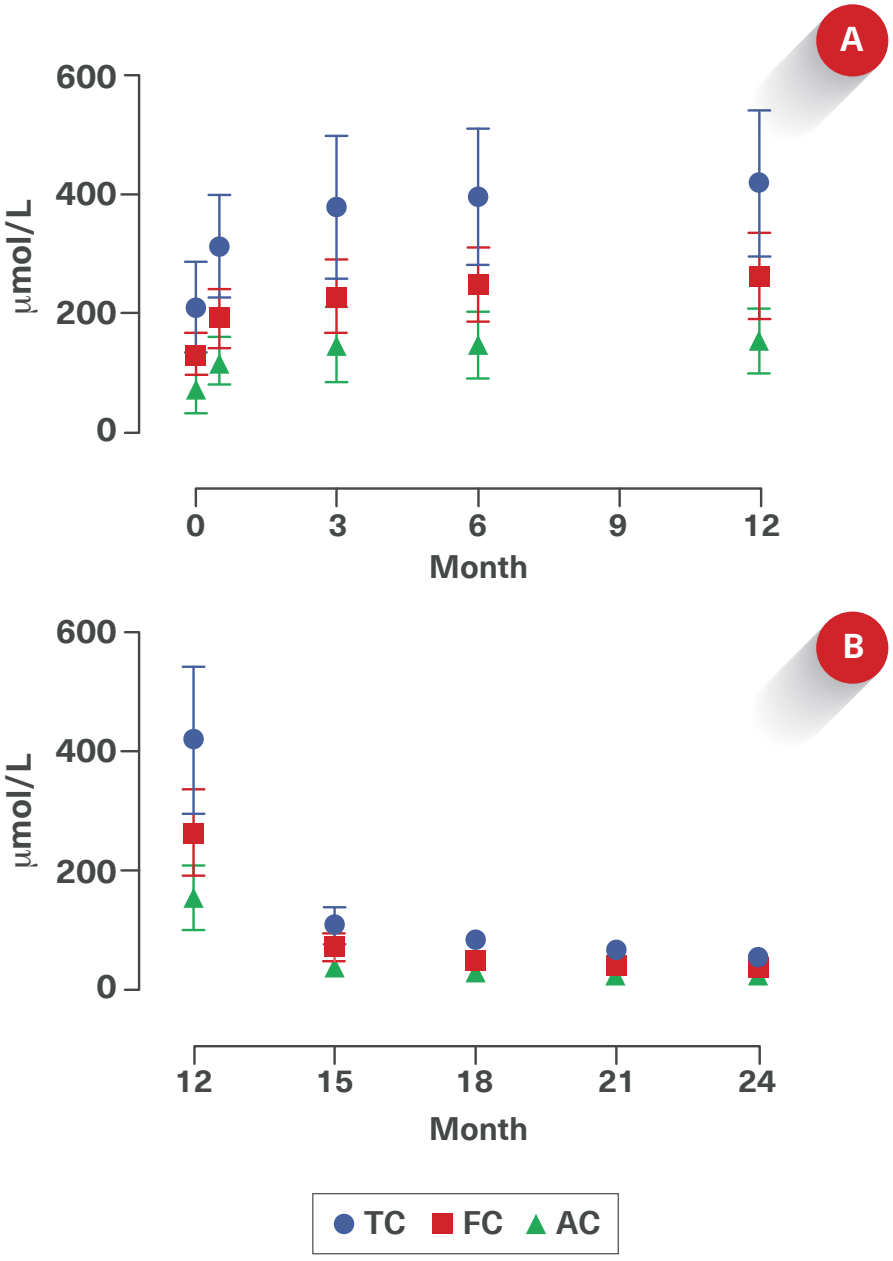
- The TC, FC, and AC levels significantly increased after 3 months upon switching to the IV mode of administration (TC, FC, AC: $p < 0.0001$) (**Figure**); however, there was no significant difference in the AC/FC ratio during the observation period ($p = 0.1739$).
- After discontinuation of carnitine administration before the dialysis, the TC, FC, and AC levels significantly decreased over 3 months, followed by slower decrease thereafter ($p < 0.0001$). The average FC value was maintained at the normal levels until 9 months, although the levels fell below the normal values when measured at the 12th month (**Figure**).

key points

L-carnitine was found to be effective as an antioxidant and in inflammatory reaction suppression, which could improve nutritional status.

After switching to an IV dosing mode, IV infusion mode resulted in well-maintained high plasma FC level as compared with that by oral administration, although the dosage was approximately half in IV infusion than in oral administration.

FIGURE Levels of TC, FC, and AC after switching to the IV mode of administration were significant as per one-way ANOVA ($p < .0001$) and Dunnett's multiple comparison tests (0 *vs* 0.5, 0 *vs* 3, 0 *vs* 6, 0 *vs* 12) (**Panel A**). Levels of TC, FC, and AC after discontinuation of carnitine administration were found to be significant according based on the results of one-way ANOVA ($p < 0.0001$) and Dunnett's multiple comparison tests (12 *vs* 15, 12 *vs* 18, 12 *vs* 21, 12 *vs* 24) (**Panel B**). TC: total carnitine; FC: free-carnitine; AC: acyl-carnitine.



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Clinical significance of different carnitine levels for improving the prognosis of patients undergoing hemodialysis

Zhang YM, Zhuo L, Hu J, et al.

Ren Fail 2016; 38(10):1654-1658

BACKGROUND AND AIM

- Carnitine deficiency worsens in patients undergoing long-term dialysis and can cause energy metabolic disorders and symptoms such as weakness, fatigue, dialysis hypotension, and muscle cramps in the short term; and angina, arrhythmia, heart failure, and limited erythropoietin effects during long-term deficiency.
- Aim of this study was to compare plasma carnitine levels in normal subjects and patients undergoing HD to determine its clinical significance and to provide a basis for carnitine supplementation in patients undergoing HD.

MATERIALS AND METHODS

- A total of 20 subjects were in the normal control group and 133 patients undergoing HD were divided into medicated (received carnitine treatment) and non-medicated groups.
- The medicated group was further divided into three subgroups according to free-carnitine (FC) level: 80-199, 200-299, and ≥ 300 μmol/L.
- Non-derivative tandem mass spectrometry was used to determine carnitine levels, and clinical symptoms such as weakness, hypotension, and muscle cramps were recorded during dialysis.

RESULTS

- The plasma FC and total carnitine (TC) levels in the non-medicated group were lower than those in the normal control group ($p < 0.05$). The acyl-carnitine (AC) level in the non-medicated group tended to be higher than that in the control group. FC, AC, and TC levels in the medicated group were higher than those in the non-medicated group ($p < 0.05$) (**Figure**).
- The medicated group had fewer symptoms during dialysis than the non-medicated group such as weakness, hypotension, and muscle cramps ($p < 0.05$). An additional comparison showed that the incidence rates of hypotension and muscle cramps in the FC < 80-199 μmol/L group were significantly lower than those in the FC ≥ 300 μmol/L medicated and non-medicated groups (**Table**).

key points

FC and TC levels in non-medicated patients undergoing HD were lower than those in the control group. The FC, AC, and TC levels of patients increased significantly after 1 g L-carnitine was administered intravenously.

Fewer clinical symptoms, such as weakness, hypotension, and muscle cramps, were observed after dialysis in patients undergoing HD in the medicated group compared to the non-medicated group.

The appropriate range of free carnitine can improve complications in patients undergoing dialysis.

FIGURE Carnitine levels in the medicated and non-medicated groups (μmol/L). Abbreviations: *Fc,* free carnitine; *Ac,* acylcarnitine; *Tc,* total carnitine.

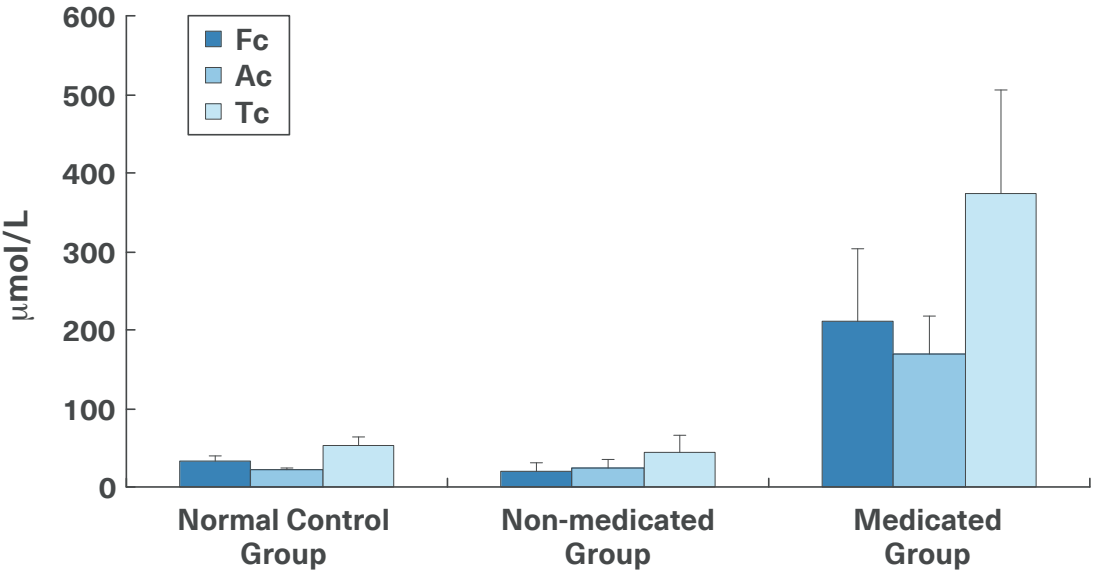

TABLE Clinical symptoms in the groups.

Groups (μmol/L)	Cases (incidence%)			
	Weakness	Hypotension	Muscle cramps	Total
Non-medicated group	26 (39.39)	33 (50.00)	39 (59.09)	66
Medicated group				
Fc = 80-199	7 (20.00)	6 (17.14)	7 (20.00)	35
Fc = 200-299	6 (33.33)	8 (44.44)	6 (33.33)	18
Fc ≥ 300	7 (50.00)	8 (57.14)	9 (64.28)	14

Fc, free carnitine

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L-carnitine supplementation and EPO requirement in children on chronic hemodialysis

Aoun B, Bérard E, Vitkevic R, et al.

Pediatr Nephrol 2010; 25(3):557-60

BACKGROUND AND AIM

- It has been suggested that excess free fatty acids secondary to L-carnitine deficiency leads to altered function of the erythrocyte sodium-potassium pump in chronic renal failure and thereby reduces erythrocyte survival time.
- It is a common finding in chronic dialysis patients to have deficiency in carnitine such patients are on a low protein diet and this molecule is easily dialyzed. L-carnitine deficiency has been correlated to the duration of dialysis.
- The aim of this study was to evaluate the effects of L-carnitine supplementation on the use of erythropoietin (EPO) requirement in pediatric hemodialysis (HD) patients.

MATERIALS AND METHODS

- This was a prospective study that included six children (three girls) without residual renal function who were on regular HD (three 4-h sessions per week) on high-flux membranes. All patients were started on intravenous L-carnitine supplementation at the same time.
- All patients received L-carnitine intravenously (2.5 g per session for patients > 30 kg and 1 g for those < 30 kg, with an average dose of 50 mg/kg per session) for a total duration of 9 months. The whole observation period was 16 months: 3 months before L-carnitine (phase 1), 9 months on L-carnitine (phase 2), and 4 months after L-carnitine withdrawal (phase 3).
- Carnitine levels (free and total) were measured by mass spectrometry, and the EPO dosage was adjusted to maintain a hemoglobin (Hb) level between 11 and 13 g/dl.

RESULTS

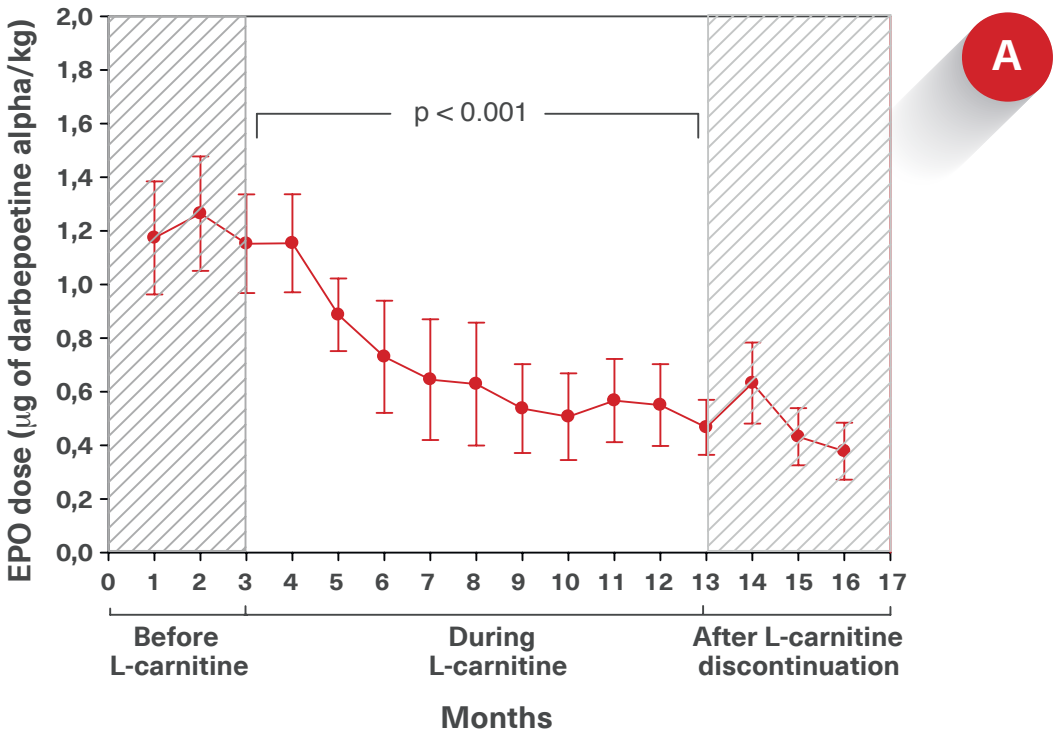
- Free carnitine blood level values were 40.4 ± 4.9 μmol/l before supplementation, 378.5 ± 77.3 μmol/l immediately after the 9-month supplementation period, and 95.6 ± 4.0 μmol/l 4 months after L-carnitine withdrawal.
- The EPO requirement before L-carnitine was 1.15 ± 0.22 (0.37-1.75) μg/kg darbepoetin alpha. During the intravenous L-carnitine supplementation period of 9 months, the EPO dose was decreased stepwise and reached 50% of the initial dose after 9 months (0.47 ± 0.10 μg/kg; $p < 0.001$) (**Figure, panel A**). All patients experienced an important reduction in EPO requirement during L-carnitine supplementation (**Figure, panel B**).
- The mean Hb level before L-carnitine supplementation was 12.9 ± 0.50 g/dl, and after the 9-month supplementation period the Hb level was unchanged. However, there was a significant increase during the first 2 months (12.2 ± 0.97 to 14.0 ± 0.54 g/dl; $p < 0.05$).

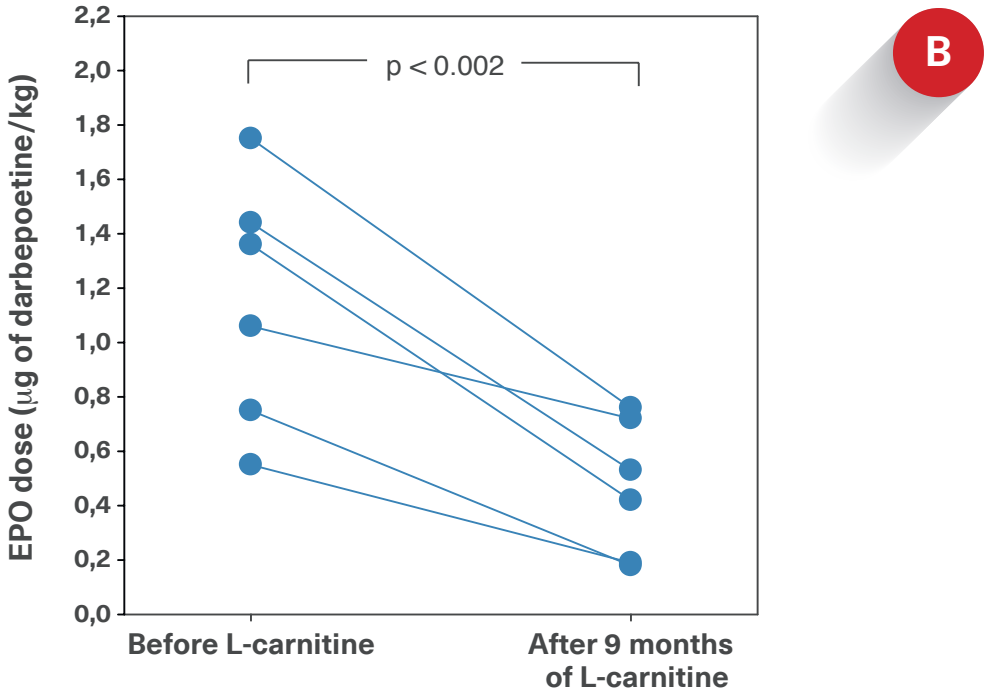
key points

Following intravenous carnitine supplementation, FC levels were higher and persisted longer than expected: this rise was associated with increased Hb levels and decreased EPO requirement.

Prospective long-term multicenter studies on a large number of patients are required to provide solid answers to the controversial question of L-carnitine supplementation in hemodialyzed children.

FIGURE **A** Erythropoietin (EPO) requirement before, during, and after intravenous L-carnitine supplementation in six hemodialyzed children. **B** Erythropoetin requirement before and at the end of the L-carnitine supplementation. Patients with a higher EPO dose had a relatively higher benefit in terms of EPO dose reduction.





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Extended duration nocturnal hemodialysis and changes in plasma metabolite profiles

Kalim S, Wald R, Yan AT, et al.

Clin J Am Soc Nephrol 2018; 13(3):436-444

BACKGROUND AND AIM

- Patients with ESRD receiving maintenance hemodialysis (HD) experience suboptimal outcomes, with mortality rates up to eight times those of the age-matched general population.
- In-center, extended duration nocturnal hemodialysis has been associated with variable clinical benefits, but the effect of extended duration hemodialysis on many established uremic solutes and other components of the metabolome was not unascertained.
- Aim of this study was to characterize changes in plasma metabolites, including several established uremic retention solutes, among individuals converting from a conventional to an extended duration HD regimen.

MATERIALS AND METHODS

- This was a post hoc analysis of a primary study, that was a 52-week prospective observational study of 37 patients who had previously received standard duration conventional HD (3-4 hours per session, three times per week) for a minimum of 90 days before recruitment and who elected to convert to in-center extended duration nocturnal HD (7-8 hours per session, three times per week).
- From this group, 33 patients who converted to nocturnal HD and 20 patients who remained on conventional HD had the available blood samples and complete datasets across 52 weeks to be included in this study.
- The primary outcomes for this study were the change in any of the 164 metabolites measured using an established metabolomic platform at baseline and after 1 year.

RESULTS

- At the 52-week follow-up, conversion to nocturnal HD resulted in a 17% increase in the urea reduction ratio ($p < 0.001$) and a 22% reduction in phosphate concentration ($p < 0.001$) compared with baseline. There was no significant change in serum albumin or normalized protein catabolic rate in either the nocturnal or control group.
- Nocturnal HD significantly reduced several nonuremic metabolites, including L-carnitine and several short-chain acylcarnitines. The reduction in L-carnitine (or "free" carnitine) is notable given that L-carnitine is already depleted in patients with ESRD undergoing standard HD (**Table**).

key points

HD intensification with extended duration nocturnal HD was associated with modest changes in metabolite profiles.

Depletion of L-carnitine, an essential cofactor in fatty acid oxidation, could have deleterious effects on cardiovascular function and could attenuate the other potentially beneficial effects of extended duration nocturnal HD.

TABLE Metabolites that significantly decreased after 1 year of extended duration nocturnal hemodialysis.

Metabolite	Nocturnal HD Final-to-Baseline Metabolite Ratio ± SD	*P Value*	Conventional HD Final-to-Baseline Metabolite Ratio ± SD	*P Value*
L-carnitine	0.82 ± 0.27	0.003	1.02 ± 0.22	0.99
Acetylcarnitine	0.75 ± 0.30	0.003	1.10 ± 0.31	0.92
α-Glycerophosphate	0.78 ± 0.50	< 0.01	1.32 ± 0.82	0.80
Phosphocreatine	0.95 ±61.73	0.003	2.24 ± 2.68	0.75
Pentose monophosphate	0.81 ± 0.85	0.01	1.40 ± 1.53	0.96
Octanoylcarnitine	0.84 ± 0.43	0.02	1.11 ± 0.53	0.96
Hexanoylcarnitine	0.87 ± 0.53	0.03	1.06 ± 0.53	0.88
Creatinine	0.95 ± 0.17	0.04	0.98 ± 0.22	0.98

Final-to-baseline metabolite ratio denotes the mean final 1-year metabolite level-to-initial baseline metabolite level ratio. P *values are calculated using the Wilcoxon rank sum test comparing metabolite level at baseline versus 1 year after multiple testing corrections (false discovery rate ,0.05). Nocturnal HD, in-center extended duration nocturnal hemodialysis; conventional HD, standard duration conventional hemodialysis.*

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L-carnitine improves gastrointestinal disorders and altered the intestinal microbiota in hemodialysis patients

Irie J, Kanno Y, Kikuchi R, et al.

Biosci Microbiota Food Health 2017; 36(1):11-16

BACKGROUND AND AIM

- Patients receiving hemodialysis (HD) manifest gastrointestinal symptoms such as constipation. The restriction of water intake and the loss of body water balance may induce constipation, and it might elevate blood urea nitrogen (BUN) level in hemodialysis patients.
- Carnitine deficiency in hemodialysis patients may be one cause of gastrointestinal discomfort and dysfunctions. However, the effects of carnitine supplementation on HD patients with gastrointestinal disorders remain to be evaluated.
- Aim of this study was to investigate the changes in the clinical symptoms, metabolic parameters, and intestinal microbiota of chronic HD patients who received L-carnitine supplementation.

MATERIALS AND METHODS

- This was a multicenter, nonrandomized, single-arm, prospective clinical trial of 15 outpatients (6 men and 9 women aged 72 ± 10 years) receiving HD in a single centre in Japan.
- L-carnitine tablets (900 mg) were administered for 3 months, and clinical and biochemical analyses were performed before and after the treatment. The frequency of passing stool per a week was counted before and after L-carnitine treatment.

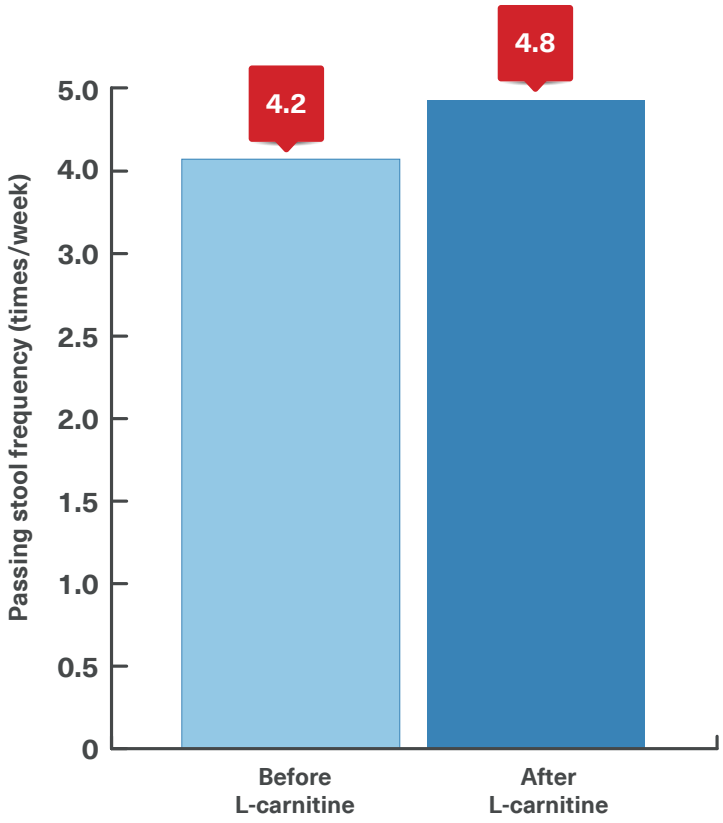
RESULTS

- The serum total carnitine level was increased significantly by supplementation with carnitine for 3 months (from 40.9 ± 2.6 μmol/l to 172.3 ± 19.0 μmol/l, $p < 0.05$). The myasthenia score was decreased significantly by the administration of L-carnitine (from 1.3 ± 0.3 to 0.8 ± 0.2, $p < 0.05$).
- The frequency of passing stool tended to increase with treatment for 3 months (from 4.2 ± 0.5 times/week to 4.8 ± 0.5 times/week; not significantly different) (**Figure**).
- Regarding the resolution of constipation, the predialysis BUN level decreased significantly after 3 months of supplementation (from 61.5 ± 4.3 mg/dl to 57.1 ± 3.3 mg/dl, $p < 0.05$). Dry weight and the increase in body weight between the patients' HD sessions (from 1.9 ± 0.1 kg to 1.8 ± 0.1 kg) were not significantly changed after supplementation, indicating that their nutritional status did not markedly change for 3 months.
- Analysis of the microbiota showed that the composition of the individual microbiota was not different between before and after supplementation, indicating that the composition of the intestinal microbiota is preserved individually.

key points

The oral supplementation of L-carnitine to the patients receiving hemodialysis improved not only their muscle discomfort but also their gastrointestinal disorders and microbiota.

FIGURE Frequency of passing stool before and after L-carnitine administration for 3 months.



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L-carnitine in peritoneal dialysis

De Vecchi AF, Arduini A, Di Liberato L, et al.

G Ital Nefrol 2011; 28(4):393-400

INTRODUCTION

- L-carnitine administration is increasingly used in dialysis patients, to compensate for dialysis losses and reduced renal synthesis. Numerous studies have evaluated the results of oral or intravenous supplementation of L-carnitine in hemodialysis, with particular regard to the effects on musculature, cardiomyopathy, intradialytic hypotension, dyslipidemia and anemia.
- Although favorable effects have been observed in many cases, some controversies and prejudices persist about the use of the compound in this patient population.

L-CARNITINE LEVELS IN PATIENTS ON PERITONEAL DIALYSIS

- Almost 40 years ago, various authors demonstrated low levels of L-carnitine in patients with peritoneal dyalisis (PD). Subsequently, other authors observed normal levels of total L-carnitine in pediatric or adult patients underwent PD. Total L-carnitine in these patients correlated significantly with body weight, total protein and triglycerides.
- In fact, in patients with PD, even in the presence of significant losses in dialysate, total L-carnitine levels are similar to controls, while those of free L-carnitine are significantly lower. This result is linked to a greater daily loss of free L-carnitine. The total/free ratio is higher in the plasma and lower in the losses of dialysis patients compared to controls.
- Furthermore, in PD, the presence of glucose in the dialysis solution and its continuous absorption from the capillaries to the mesenteric veins cause a continuous stimulation of insulin production, with an increase in insulin tolerance, hyperglycemia or even diabetes.

CLINICAL RESULTS OF THE ADMINISTRATION OF L-CARNITINE IN PATIENTS ON PERITONEAL DIALYSIS

- In peritoneal dialysis, the small number of published papers provided controversial results as well. Some authors observed significant lowering of apolipoprotein B without changes in cholesterol, triglycerides, free fatty acids, phospholipids and apoliporotein A after administration for short periods of high-dose oral L-carnitine to adult or, more often, pediatric patients.
- Others did not observe any positive effect. *In vitro* studies demonstrated that peritoneal dialysis solutions containing L-carnitine cause less damage to mesothelial and endothelial cells than glucosebased-only peritoneal dialysis solutions.
- More recently, L-carnitine was used as an osmotic agent in experimental dialysis solutions for human use: the peritoneal ultrafiltration was similar to that induced by glucose solutions. In addition, intraperitoneal administration allows the measurement of absorbed carnitine, thus establishing a correct dose/effect ratio.

key points

In PD patients, L-carnitine could play a fundamental role in improving glucose dysmetabolism linked to continuous glucose loading and could improve the "physiology" of the dialysis solution, reducing the progressive fibrosis of the peritoneal membrane.