

SECONDARY CARNITINE DEFICIENCY IN DIALYSIS PATIENTS: SHALL WE SUPPLEMENT IT?

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MEETING SUMMARY

Carnitine, essential for fatty acid β -oxidation, is obtained from diet and through *de novo* biosynthesis. The organic cation/carnitine transporter 2 (OCTN2) facilitates carnitine cellular transport and kidney resorption. Carnitine depletion occurs in OCTN2-deficient patients, with serious clinical complications including cardiomyopathy, myopathy, and hypoketotic hypoglycaemia. Neonatal screening can detect OCTN2 deficiency. OCTN2-deficiency is also known as primary carnitine deficiency. Carnitine deficiency may result from fatty acid β -oxidation disorders, which are diagnosed via plasma acylcarnitine profiling, but also under other conditions including haemodialysis.

Given the importance of the kidney in maintaining carnitine homeostasis, it is not unexpected that long-term haemodialysis treatment is associated with the development of secondary carnitine deficiency, characterised by low endogenous L-carnitine levels and accumulation of deleterious medium and long-chain acylcarnitines. These alterations in carnitine pool composition have been implicated in a number of dialysis-related disorders, including erythropoietin-resistant renal anaemia. The association between erythropoietin resistance and carnitine levels has been demonstrated, with the proportion of medium and long-chain acylcarnitines within the total plasma carnitine pool positively correlated with erythropoietin resistance. Recent research has demonstrated that carnitine supplementation results in a significant reduction in erythropoietin dose requirements in patients with erythropoietin-resistant anaemia.

Few studies have been conducted assessing the treatment of carnitine deficiency and haemodialysis-related cardiac complications, particularly in children. Thus, a study was recently conducted which showed that intravenous carnitine in children receiving haemodialysis significantly increased plasma carnitine

levels and improved the acylcarnitine to free carnitine ratio. Cardiac function was also significantly improved (determined by longitudinal strain rate using speckle-tracking echocardiography). A study in children receiving continuous renal replacement therapy (CRRT) showed that prevalence of carnitine deficiency increased with the time on CRRT. The impact of carnitine deficiency resulting from CRRT is not well known, although it has been associated with increased mortality in critically ill children. An ongoing, randomised controlled clinical trial is assessing the impact of carnitine supplementation on myocardial function in children receiving CRRT.

Thus, carnitine deficiency is a disorder with significant clinical impact, particularly in patients undergoing renal replacement therapy, which can be simply diagnosed. Carnitine supplementation can be used to effectively treat carnitine deficiency.

Carnitine Metabolism in Human Health and Disease Notably in Genetic Metabolic Diseases

Professor Doctor Ronald J.A. Wanders

Carnitine Biosynthesis and Homeostasis

Carnitine was first discovered in muscle extracts in 1905.¹ Subsequently, Dr G. S. Fraenkel discovered a key role of carnitine through his study of insects and found that carnitine is essential for the beetle *Tenebrio molitor*. Experimentally, excluding carnitine from culture medium resulted in the death of beetle larvae and accumulation of fat was noted. This observation was the first evidence that

carnitine may have a role in fatty acid oxidation. In 1955, Dr I. B. Fritz demonstrated that carnitine stimulates fatty acid oxidation, and it has since been established that fatty acid β -oxidation is fully dependent on carnitine.¹

Humans obtain carnitine from several major dietary sources (meat, fish, and dairy products), and can also biosynthesise carnitine from the amino acid lysine.¹ For omnivores, 75% of body carnitine originates from the diet. In contrast, vegetarians and vegans need to biosynthesise >75% of their body carnitine and may have low carnitine levels as a result. The *de novo* synthesis of carnitine involves four enzymatic steps and is shown in Figure 1.¹

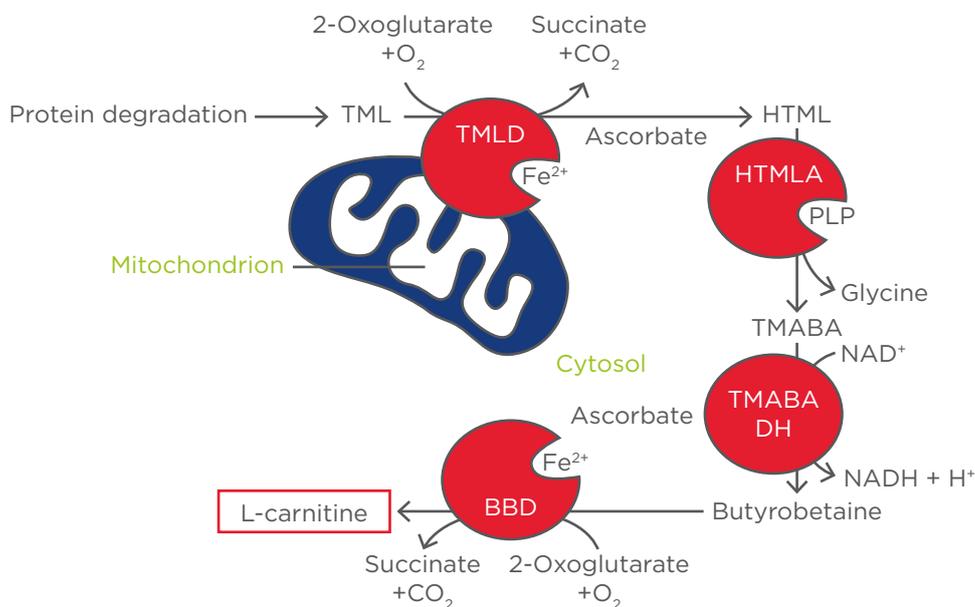


Figure 1: Carnitine biosynthesis.¹

BBD: γ -butyrobetaine dioxygenase; HTML: β -hydroxy- ϵ -N-trimethyllysine; HTMLA: β -hydroxy- ϵ -N-trimethyllysine aldolase; TMABADH: γ -trimethylaminobutyraldehyde dehydrogenase; TML: ϵ -N-trimethyllysine; TMLD: ϵ -N-trimethyllysine dioxygenase; PLP: pyridoxal 5'-phosphate; NAD: nicotinamide adenine dinucleotide.

Adapted from Vaz FM and Wanders RJ.¹

Importantly, humans have a low capacity for carnitine synthesis. Moreover, this biosynthetic process proceeds at a fixed rate and cannot be induced to produce more carnitine.

Carnitine homeostasis in humans reflects the balance between *de novo* synthesis and dietary uptake, with loss via urine and faeces. The protein OCTN2 plays a crucial role in carnitine homeostasis. This plasma membrane-based protein actively facilitates the sodium-dependent transport of carnitine from the plasma (typical carnitine concentrations 20–40 $\mu\text{mol/L}$) to the cytosol of cells (typical carnitine concentrations $>2,000 \mu\text{mol/L}$) in all tissues. In the kidney, OCTN2 activity also results in carnitine resorption.

Functions of Carnitine

Carnitine has several important physiological functions in humans. An essential role for carnitine is in fatty acid β -oxidation in the mitochondria, known as the carnitine cycle (Figure 2). In carnitine deficiency, this carnitine cycle is unable to complete effectively.

Carnitine is also involved in the transfer of peroxisomal fatty acid β -oxidation end-products

to the mitochondria for full oxidation to carbon dioxide and water.¹ The third role of carnitine is to remove acyl-coenzyme (CoA) species from the mitochondria and the cell. This function is very important as it is the only way to remove acyl-CoA, which is deleterious to cells. Within mitochondria, acyl-CoA is converted to acyl-carnitine which is transported out of the cells by carnitine-acyl-carnitine translocase (mitochondrion membrane) and OCTN2 probably via one of the OCTNs in the plasma membrane. Plasma acyl-carnitine is then excreted via urine and faeces.

Carnitine-Related Disorders

To date, only a few disorders of carnitine biosynthesis have been identified. The most frequently occurring condition is OCTN2 deficiency, a genetic disorder involving the gene *SLC22A5*, which codes for OCTN2.¹ Deficiency of OCTN2 has several manifestations, in particular, defective carnitine uptake into cells and resorption by the kidneys. Consequently, plasma carnitine concentrations are low ($<1 \mu\text{mol/L}$) and urinary carnitine levels are high. Critically, fatty acid β -oxidation is impaired in virtually all tissues.

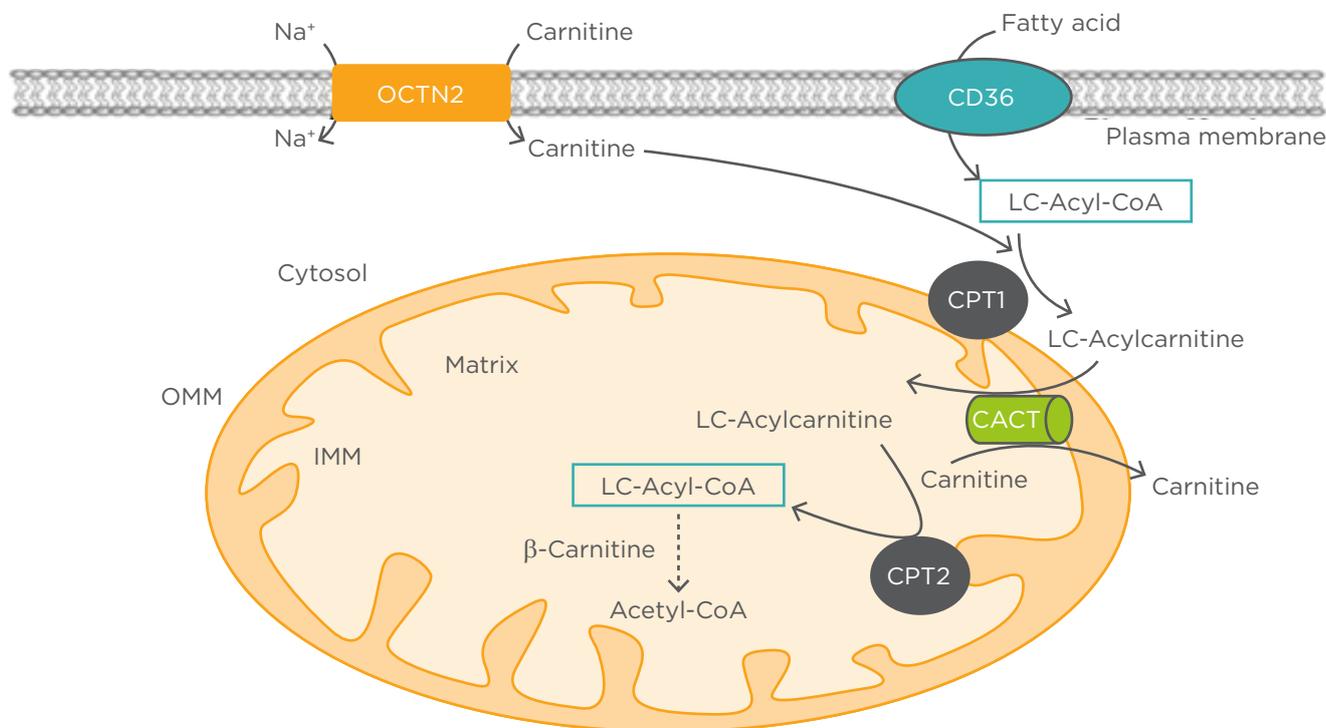


Figure 2: The carnitine cycle.

CACT: carnitine-acyl-carnitine translocase; CoA: coenzyme A; CPT: carnitine palmitoyl transferase; LC: long chain; OCTN2: carnitine/organic cation transporter 2; OMM: outer mitochondrial membrane; IMM: inner mitochondrial membrane.

Clinical signs and symptoms of OCTN2 deficiency are variable and wide ranging. In early-onset presentation of this condition, the following can occur: acute metabolic decompensation, hypoketotic hypoglycaemia, Reye's syndrome, and sudden infant death.¹ Presentation of OCTN2 deficiency later in life is more insidious with chronic myopathy, with or without muscle weakness, which may result in sudden (cardiac) death.

A key challenge facing clinicians is to identify patients with OCTN2 deficiency as soon as possible, ideally through neonatal screening.² Diagnosis is important as carnitine therapy is lifesaving, and can correct clinical signs and symptoms of carnitine deficiency. The first neonatal screen for an inborn error of metabolism was pioneered by Dr Guthrie, who developed a test for phenylketonuria in a dried blood spot. Currently, the newborn heel prick, utilising a Guthrie card, is routinely used for screening numerous metabolic diseases, including a range of fatty acid oxidation disorders. Testing for OCTN2 deficiency using this method is available in the USA and in some European countries.

Many inborn errors of fatty acid β -oxidation are known.² One of the most frequent deficiencies is a defect in medium chain acyl-CoA dehydrogenase (MCAD). This enzyme catalyses the first step in the degradation of octanoyl-CoA (C8:0-CoA) and decenoyl-CoA (C10:1-CoA) to carbon dioxide and water, and ketone bodies. When MCAD is deficient, C8:0-CoA and C10:1-CoA build up in the mitochondria. Subsequently, C8:0-carnitine and C10:1-carnitine levels are increased in the plasma and urine. Profiling plasma acylcarnitines provides valuable insight into which enzymes and/or transporters are defective in fatty acid β -oxidation.² The diagnosis is then confirmed by enzymatic and molecular analyses. Carnitine deficiency can also occur secondary to other conditions or illnesses, the best described of which is dialysis-related carnitine deficiency, which is detailed in the coming section.

Characteristics of Dialysis-Related Carnitine Deficiency: Effectiveness of L-Carnitine for the Treatment of Erythropoietin-Resistant Renal Anaemia

Doctor Stephanie E. Reuter

The kidney has a critical role in carnitine homeostasis through the maintenance of normal

endogenous carnitine levels.³ Given its low molecular weight and polarity, carnitine is extensively filtered at the glomerulus, but then undergoes extensive saturable resorption in the proximal convoluted tubule to avoid extensive loss into the urine. Whilst haemodialysis provides a valuable replacement for kidney function in end-stage renal disease (ESRD), it is unable to compensate for all homeostatic mechanisms and, in the case of carnitine, results in the development of dialysis-related carnitine deficiency.

Dialysis-Related Carnitine Deficiency

The impact of haemodialysis on endogenous carnitine levels has been established, with a single 3-hour dialysis session found to result in a substantial (74%) reduction in plasma L-carnitine concentrations during the intra-dialytic period.⁴ However, in the 2-day inter-dialytic period, plasma L-carnitine levels were restored as body carnitine levels re-equilibrated and L-carnitine moved out of the tissue stores and replenished the plasma carnitine pool. Whilst a 74% loss of a plasma L-carnitine pool that only comprises <1% of total body carnitine is unlikely to significantly impact on carnitine pool composition following a single dialysis session, ongoing 3-times per week haemodialysis over an extended period would result in substantial changes in the endogenous carnitine pool, particularly in a setting with decreased dietary intake and a protein-restricted diet, along with a reduction in carnitine biosynthesis by the damaged kidney.

The relationship between dialysis age and carnitine concentrations was subsequently examined in patients with ESRD during the first year of haemodialysis treatment and in the longer term (>12 months).⁵ During the first year of dialysis, plasma carnitine levels declined significantly from baseline levels, with the majority of change occurring within the first few months. Concentrations continued to decline with increasing dialysis age, such that all long-term haemodialysis patients had plasma L-carnitine levels below that previously established for healthy controls (Figure 3).^{5,6} Examination of muscle L-carnitine concentrations also indicated a significant decline with increasing time on dialysis treatment.

Previous research has demonstrated that administration of intravenous L-carnitine at the end of each dialysis session results in the

replenishment of total body carnitine stores.⁴ As expected, haemodialysis results in a substantial clearance of exogenous carnitine. However, carnitine administration at the end of dialysis resulted in a pharmacokinetic profile consistent with the distribution of exogenous carnitine into the peripheral compartments and incorporation into the tissue stores. This has subsequently been illustrated using pharmacokinetic modelling.⁷

Interestingly, in these previous studies it was noted that whilst plasma L-carnitine levels were substantially affected by haemodialysis treatment, total plasma carnitine concentrations (i.e. L-carnitine and the sum of all acylcarnitines) were relatively unaffected. Examination of the relative compositions of the endogenous plasma carnitine pool in haemodialysis patients indicated that haemodialysis treatment is associated with not only loss of L-carnitine, but also accumulation of medium and long-chain acylcarnitines.⁵ Strikingly, in long-term haemodialysis patients, these carnitine esters comprise approximately 25% of the total plasma carnitine pool, compared with negligible levels in healthy controls (Figure 4).

Examination of the pattern of acylcarnitine accumulation with haemodialysis treatment indicated that 29 out of 31 individual acylcarnitines quantified were significantly higher in long-term haemodialysis patients compared with healthy controls.⁸ Furthermore, the dialytic removal of acylcarnitines was inversely related to carbon-chain length of the carnitine ester, such that the longest acylcarnitines were not removed at all by dialysis. This is likely a result of increasing molecular size and increased protein binding associated with increasing carbon chain length.

Clinical Relevance of Dialysis-Related Carnitine Deficiency

In patients receiving long-term haemodialysis treatment, perturbation of carnitine homeostasis has been linked to several common dialysis-related conditions such as erythropoietin-resistant renal anaemia, cardiac dysfunction, dialytic symptoms (muscle fatigue, asthenia, cramps), and poor quality of life.⁹ In December 1999, based on the above data establishing the development of dialysis-related carnitine deficiency, levocarnitine (Carnitor®, Sigma-Tau Pharmaceuticals, Gaithersburg, MD, USA) was approved by the US Food and Drug Administration (FDA) for the prevention and treatment of carnitine deficiency in patients with

ESRD receiving dialysis treatment. Following this FDA approval, consensus guidelines, developed in September 2002 by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI), recommended intravenous L-carnitine supplementation for the treatment of a number of dialysis-related conditions.¹⁰ Additionally, intravenous L-carnitine received coverage by the US Centers for Medicare and Medicaid Services for the treatment of erythropoietin-resistant anaemia and/or intradialytic hypotension in carnitine-deficient patients receiving long-term haemodialysis treatment.¹¹ However, the benefit of L-carnitine supplementation for these conditions remains a matter for debate.

Extensive research has been conducted examining the potential benefit of L-carnitine as an adjunct for the treatment of renal anaemia.⁹ Whilst most studies have demonstrated improvements with respect to haematocrit or erythropoietin dose, many were poorly designed with short treatment periods, small sample sizes, and/or uncontrolled/unblinded study designs. Furthermore, a number of studies employed the use of oral L-carnitine, a treatment option that is not recommended due to poor bioavailability, potential accumulation of trimethylamine-N-oxide from the gastrointestinal biodegradation of carnitine to trimethylamine, and possible acylation of L-carnitine during oral absorption. Interestingly, from these studies some authors noted that some patients 'responded' better to carnitine supplementation whilst others did not. Amongst a number of possible explanations, it was proposed that the patients who exhibited a greater response to carnitine treatment were those who displayed more disturbed carnitine profiles.

To explore this further, the relationship between endogenous plasma carnitine pool composition and erythropoietin requirements were assessed in long-term haemodialysis patients.¹² In order to consider both erythropoietin dose and effectiveness of that dose, the erythropoietin resistance index (ERI) was determined for each patient, calculated as dose/kg/week/g haemoglobin (Hb); based on NKF practice recommendations erythropoietin resistance was defined as $>0.02 \mu\text{g}/\text{kg}/\text{week}/\text{g Hb}$. A significant negative correlation between ERI and plasma L-carnitine levels was demonstrated, such that all patients classified as erythropoietin resistant exhibited subnormal L-carnitine levels ($<30 \mu\text{M}$).

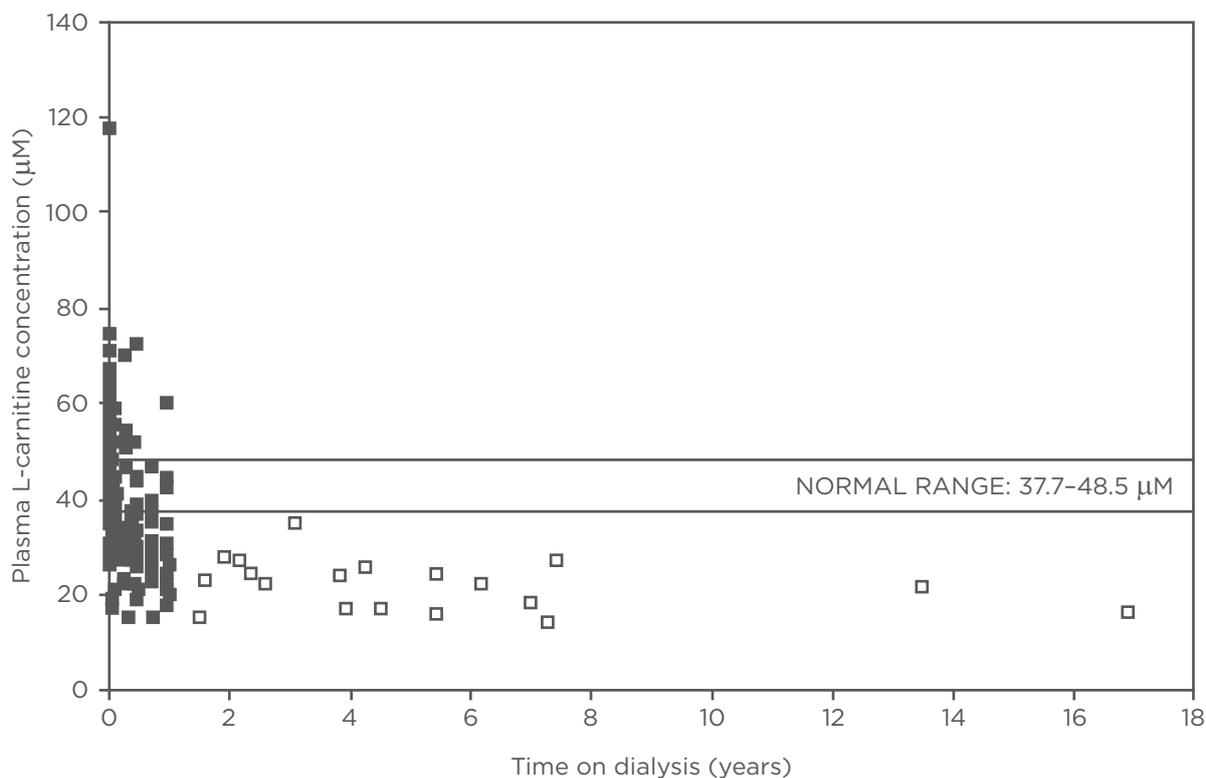


Figure 3: Long-term effect of haemodialysis on plasma carnitine concentrations.⁵

Endogenous plasma L-carnitine concentrations as a function of dialysis age in longitudinal patients during the first 12 months of haemodialysis treatment (solid squares) and in single-session patients having received dialysis for >12 months (open squares).

A stronger positive correlation between ERI and the proportion of medium and long-chain acylcarnitines within the total plasma carnitine pool was found, thereby indicating that a more disturbed carnitine profile is associated with erythropoietin resistance. Whilst the exact mechanism needs to be fully elucidated, it is proposed that this is mediated through effects on carnitine palmitoyltransferase (CPT) activity, an important enzyme involved in the incorporation of fatty acids into the erythrocyte membrane. Previous studies have illustrated that CPT can be regulated by carnitine and acylcarnitine levels, such that high levels of L-carnitine increase CPT activity whereas acylcarnitine inhibits CPT. Feasibly, the pattern of secondary carnitine deficiency seen in long-term haemodialysis treatment would result in inhibition of CPT by high acylcarnitine levels, which is not counteracted by the low levels of L-carnitine. This would conceivably lead to decreased acyl trafficking and reduced erythrocyte membrane repair and stabilisation. It is hypothesised that administration of L-carnitine in haemodialysis would result in a better balance of CPT activity thereby increasing the lifespan of the

erythrocyte, providing an adjunct to erythropoietin in the treatment of anaemia.

Interestingly, only one published study has assessed the benefit of L-carnitine supplementation for renal anaemia in a specific group of patients who exhibit erythropoietin-resistance. However, this study employed a non-controlled, open-label assessment of oral L-carnitine. Recently, a randomised, double-blind, placebo-controlled study (ACCORD [Assessment of Carnitine for Clinical Outcomes in Renal Disease]) examined the effect of intravenous L-carnitine administration (20 mg/kg after each dialysis session for 6 months, or a matched placebo) in a group of patients classified as erythropoietin-resistant (>0.02 µg/kg/week/g Hb). L-carnitine treatment was shown to result in a significant improvement in erythropoietin requirements over time (~40% reduction), an effect that was significantly greater than that seen in placebo-treated patients (publication submitted for consideration). These results provide compelling evidence for the use of L-carnitine for the treatment of erythropoietin-resistant anaemia. Further studies examining the potential benefit of

L-carnitine for other dialysis-related conditions is currently being conducted.

Carnitine Levels and Myocardial Function in Children Receiving Chronic Haemodialysis

Professor Doctor Asha Moudgil

Children with ESRD receiving chronic haemodialysis are at risk for carnitine deficiency and cardiac complications. Since carnitine is essential for cardiac muscle function, carnitine deficiency in children may contribute to cardiac complications and supplementation may help improve cardiac function.

Improved Cardiac Function with Carnitine

In adults receiving chronic haemodialysis, oral^{13,14} and intravenous^{15,16} carnitine treatment improved ejection fraction (a marker of systolic left ventricular [LV] function), and intravenous carnitine supplementation improved myocardial fatty acid imaging.¹⁷ Few studies have investigated the effect of carnitine supplementation on cardiac function

in children receiving haemodialysis, with mixed results. Oral carnitine was shown to improve some measures of LV function in two studies,^{18,19} intravenous carnitine supplementation did not improve cardiac function as measured by standard echocardiography in another study.²⁰

In a prospective, longitudinal, pilot study, we recruited patients (n=9) aged 2–21 years with ESRD and receiving haemodialysis for ≥3 months, on a stable erythropoietin dose and no underlying heart disease.²¹ The study included a 3-month observation phase (no carnitine) followed by a 6-month intravenous carnitine (20 mg/kg/dialysis treatment) intervention phase. The retrospective control group (n=8) consisted of children receiving chronic haemodialysis (no carnitine supplementation) with data from two echocardiograms (≥6 months apart).

Patient demographics and baseline clinical characteristics were similar between groups. In the study group, pretreatment total carnitine and free carnitine plasma levels were low; mean (standard error of the mean [SEM]) values were 49 μmol/L (1.7) and 29 μmol/L (1.2), respectively.

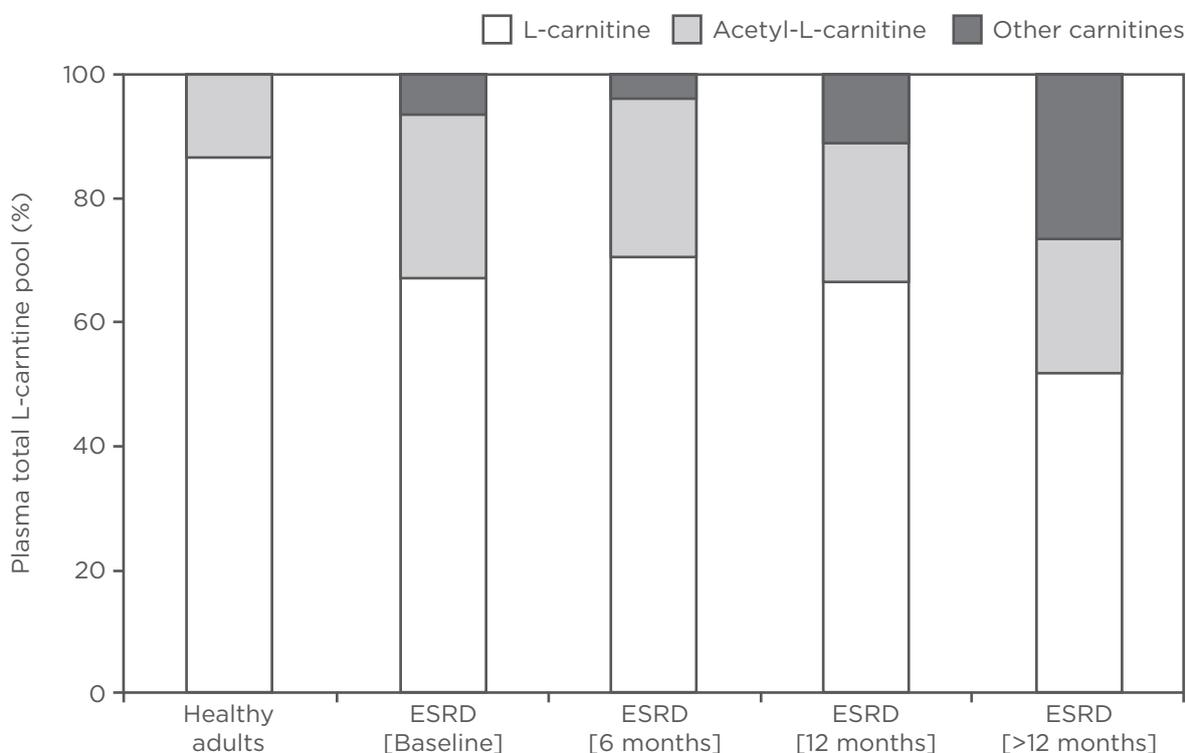


Figure 4: Impact of haemodialysis on plasma carnitine pool composition.⁵

Relative composition of the endogenous plasma carnitine pool in healthy controls and end-stage renal disease (ESRD) patients prior to commencing haemodialysis treatment (baseline) and after undergoing haemodialysis treatment for 6, 12, and >12 months.

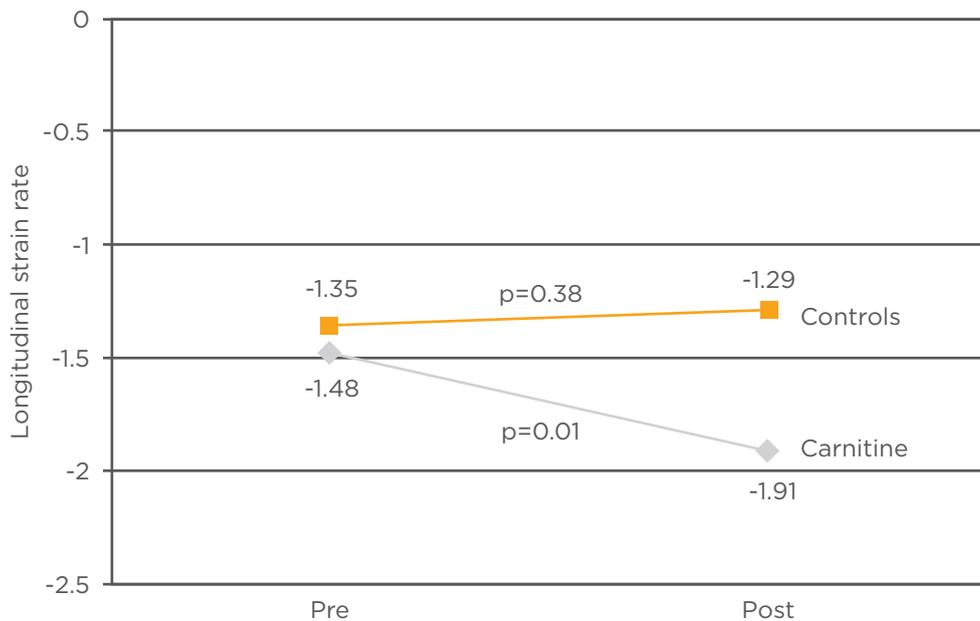


Figure 5: Longitudinal strain rate pre and post-carnitine treatment in children receiving haemodialysis.

After carnitine supplementation, total and free carnitine levels were markedly higher versus pretreatment; mean (SEM) values were 298 $\mu\text{mol/L}$ (31.8) and 180 $\mu\text{mol/L}$ (19.2), respectively, both $p < 0.0001$.²¹ Moreover, the acylcarnitine to free carnitine ratio was significantly reduced post-treatment versus pretreatment (mean \pm SEM: 0.73 ± 0.04 versus 0.65 ± 0.05 ; $p = 0.02$), although this ratio was not reduced to normal values.

No differences in LV function were seen in standard echocardiograms between the pre and post-carnitine treatment phases in the study group. However, with speckle-tracking echocardiography (a novel and sensitive technique that evaluates myocardial motion in three planes), the longitudinal strain rate was significantly improved by 33% with carnitine supplementation versus pretreatment values (mean \pm SEM: -1.91 ± 0.12 versus -1.48 ± 0.11 , respectively; $p = 0.01$) (Figure 5). For this parameter, a more negative value equates to improved heart contractibility. In contrast, longitudinal strain rate in the control group was not significantly different between assessments (mean \pm SEM: -1.35 ± 0.13 versus -1.29 ± 0.09 , respectively; $p = 0.38$). Overall, this study showed that in children receiving chronic haemodialysis, intravenous carnitine supplementation for 6 months improved plasma carnitine levels and improved LV function as measured by speckled tracking.²¹

Carnitine Deficiency in Continuous Renal Replacement Therapy

Carnitine homeostasis has not been well-studied in CRRT. Children receiving CRRT are highly likely to be carnitine deficient due to constant carnitine removal by CRRT; lack of production by the kidney and/or the liver; no dietary carnitine intake; and comorbidities associated with critical illness known to deplete carnitine (e.g. sepsis, muscle wastage, systemic inflammatory response syndrome). Preliminary data from a pilot study on the kinetics of carnitine removal in adults receiving continuous veno-venous haemofiltration (CVVH) indicated complete passage and efficient removal of free carnitine through the CVVH membrane, based on calculated sieving coefficients.²² Carnitine deficiency, dyslipidaemia, and muscle catabolism were reported in a case report of a critically ill adult receiving CRRT for 4 months.²³

Carnitine deficiency in children and young adults ($n = 42$; 0–26 years old) with acute kidney injury receiving CRRT was assessed in a recent study at Children’s National Health System in Washington DC, USA.²⁴ Mean (SEM) age was 7.9 years (1.1), 52% of recruited patients were male, and the mean (SEM) length of stay in the intensive care unit was 68.9 days (10.4). The range of the Paediatric Logistic Organ Dysfunction score was 2–19 (on a scale of 0–33). At baseline, approximately one-third of patients had carnitine deficiency: mean (SEM) for free carnitine was

25.2 $\mu\text{mol/L}$ (4.4).²⁴ The proportion of carnitine-deficient patients (based on free carnitine plasma levels) was 70%, 90%, and 100% at Weeks 1, 2, and 3 of CRRT, respectively. Seventy-two percent of patients died. The odds ratio for death, adjusting for age, sex, and race, was 4.9 ($p=0.03$) based on free carnitine deficiency versus patients with normal carnitine levels. Thus, carnitine deficiency occurs rapidly in children receiving CRRT, and is associated with increased mortality.²⁴

Currently, a clinical trial is in progress (NCT01941823) to compare the effects of carnitine supplementation (Carnitor at 20 mg/kg/day, intravenously) in children (1-17 years old) receiving CRRT with those not receiving carnitine (control). The key outcome measures are cardiac function and prevalence of carnitine deficiency.

Summary and Conclusions

Overall, the evidence demonstrates that carnitine is essential to human health. Although carnitine can be synthesised *de novo*, this capability is limited and dietary sources are crucial in maintaining carnitine body stores in healthy humans. Carnitine has several key roles, particularly

in fatty acid β -oxidation and detoxification of resulting end products within the cell, as well as the removal of deleterious acyl-CoA species.

Primary carnitine deficiency arises from certain genetic defects, such as in OCTN2 and fatty acid, and amino acid oxidation pathways. Secondary carnitine deficiency results from other conditions/illness, the most well-studied of which is kidney failure and dialysis. Patients with ESRD receiving long-term haemodialysis have significant disruption of carnitine homeostasis with reduced plasma and tissue carnitine, and increased proportions of deleterious medium and long-chain acyl carnitines in the plasma. Similar disruptions occur in patients receiving CRRT. Carnitine deficiency, regardless of cause, has many clinical manifestations including erythropoietin-resistant renal anaemia, and cardiac dysfunction, particularly in children.

Carnitine deficiency is easily diagnosed either by early screening (in the case of primary deficiency) or by monitoring plasma carnitine levels in patients known to be at high risk, such as those receiving renal replacement therapy. Based on the clear evidence to date, carnitine deficiency, regardless of cause, should be treated with carnitine supplementation.

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