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L-carnitine for anemia in hemodialysis patients: A last resort

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L-Carnitine for Anemia in Hemodialysis Patients: A Last Resort

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In this issue of the *Clinical Journal of the American Society of Nephrology*, Mercadal and colleagues address whether the biologically active form of carnitine, L-carnitine (LC), offers an adjuvant erythropoietic effect to patients with newly diagnosed ESRD undergoing maintenance hemodialysis (1). Their hypothesis, addressed in the CARNIDIAL trial (NCT 00322322) stems from abundant clinical and bioscientific data that have suggested a multiplicity of salutary effects of LC in the anemia of CKD.

LC is a dialyzable, 162-D quaternary amine that is not bound to albumin in plasma and is stored primarily in muscle. It is also known as vitamin B_T (T for the *Tenebrio* species) after its discovery as a mealworm growth factor in 1952 (2). It is the product of the multistep metabolism of 6-N-trimethyllysine. Carnitine production may also be driven by the ingestion of certain foodstuffs after its methylated precursor is liberated from proteins during normal digestion, in particular, milk and red meat (hence its name). Nutritional supplements of carnitine abound. The biosynthesis of LC in humans takes place principally in the kidney and liver, a vitamin C–dependent process.

After cellular entry, LC transports cytosolic fatty acids into the mitochondrion for β oxidation to acetyl coenzyme (CoA) and is thus a regulator of ketogenesis. The parent molecule is first acylated to acylcarnitine with acyl CoA by carnitine acyltransferase I, which is localized to the outer mitochondrial membrane. Subsequently, the acylated moiety is translocated into the mitochondrial matrix by a specific translocase, resident on the outer mitochondrial membrane. Finally, acylcarnitine, *via* the inner mitochondrial membrane carnitine acyltransferase II, returns as carnitine to the cytosol as acyl CoA becomes engaged in β oxidation to acetyl CoA and, from there, to liberation of energy through the tricarboxylic acid cycle. Aside from its energy-productive role, especially in kidney, liver, brain, and skeletal muscle, LC has potentially beneficial roles in the maintenance of bone mass and mitigation of oxidant stress. Acting as an antioxidant, LC may reduce lipid peroxidation, thereby reducing potential cellular membrane damage during oxidant stress (3,4).

Plasma levels of LC are less than one tenth tissue levels, and active transport of LC into tissues takes place. The turnover time in kidney is approximately 24 minutes. Plasma LC levels—both free and total—among patients who have not yet reached ESRD may be elevated (4–6). However, there is a depression of the free-to-total LC level in patients undergoing hemodialysis, and levels may decrease 75% during a hemodialysis session because both moieties are dialyzable (7). With time, free and total plasma levels decline in patients receiving maintenance hemodialysis, thereby reducing plasma free-to-total carnitine (free and acylated forms) and free carnitine-to-acylcarnitine ratios (8). Correspondingly, skeletal muscle–free LC in hemodialysis patients may decrease (9,10). Because gut absorption of carnitine is unimpaired (11), reversal of this deficiency by oral supplementation is biologically plausible and reasonable.

Many mechanisms have been attributed as causative with regard to the beneficial effects of LC in the anemia of CKD. In CKD, erythrocyte, cellular free levels are elevated, and the total carnitine level is normal, increasing the free-to-total carnitine ratio (12). However, were LC deficiency to occur, several mechanisms might contribute to the anemia of CKD. Reduced membrane stability and enhanced osmotic fragility, with a consequent reduction of red cell half-life and suboptimal reticulocytosis, could conspire to reduce hematocrit even beyond the reduction due to erythropoietin deficiency (13). Before the erythropoietin-stimulating agent (ESA) era, Albertazzi (14) and Trovato (15) and their colleagues observed that LC supplementation (1 g/d) increased hematocrit and reticulocyte counts in their respective studies of 12 hemodialysis patients observed for 6 months and a separate, small, 12-month, double-blind, placebo-controlled trial. In Trovato and colleagues' study (15), all 46 participants were adequately treated with folic acid, vitamin B12, and ferric gluconate at the terminus of each hemodialysis session. LC supplementation was administered per protocol, and the 24% mean hematocrit at baseline decreased 2%; in the treatment group, hematocrit increased 12% without the benefit of ESA treatment.

Later, in ESA-treated patients, Kooistra and colleagues observed that the total LC and free levels demonstrated an inverse relationship with hematocrit in maintenance hemodialysis patients (16). In their study, LC demonstrated a beneficial effect in patients with hematocrit <30%. However, contradictory studies challenging the utility of LC in treating anemia in hemodialysis patients emerged (17,18). Caruso and colleagues established no overall effect of LC on hemoglobin levels after 6 months of treatment in their trial (18). LC-treated

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elderly patients required a lower recombinant human erythropoietin (rHuEPO) dose to maintain their hematocrit levels up to 3 months after trial termination compared with patients in the control group of similar age.

Moreover, salutary effects of LC on *in vitro* measurements of osmotic resistance and mechanical stability have been documented by Matsumura and Arduini and their colleagues (19,20). Finally, LC enhances rat erythrocyte membrane Na/K adenosine triphosphatase activity. This potentially offsets the blunted activity of this electrogenic pump by the uremic milieu, which may foster reduced cell survival. In maintenance hemodialysis patients, LC, by enhancing mitochondrial delivery of free fatty acids to red cells, would reverse the slowing of the pump by these accumulating substrates and promote membrane integrity (21,22).

In CARNIDIAL, the rHuEPO resistance index (EPO-RI)—a ratio that expresses treatment effectiveness in units of rHuEPO normalized to body weight to hemoglobin concentration—was ascertained in a 1-year trial involving 92 incident hemodialysis patients. The investigation, the first of its kind, was conducted in a multicenter, randomized, double-blind, placebo-controlled fashion. Of the 46 patients randomly assigned to the placebo group, there were 38 completers (83%). In the carnitine group, LC was administered prophylactically to patients with a dialysis vintage of just 40 days; there were 35 completers (76%). Of note, placebo recipients experienced just an 11% reduction in LC levels by month 12 of the study, less than the anticipated 20%–30% decline (5,12). The levels of LC declined modestly in the untreated group, and LC levels were nearly five times those of the untreated group by 3 months. Nutritional equivalence, with plasma albumin concentration used as the benchmark, was otherwise achieved throughout the study. The investigators did not perform tertile or quartile trend analysis of the EPO-RI.

The demographically similar carnitine group received 1 g of intravenous LC or approximately 14.5 mg/kg, a dose that had been previously established to maintain LC levels within the normal range (23). At baseline, this group had mildly lower plasma levels of albumin and hemoglobin but a greater C-reactive protein concentration and rHuEPO dose. However, after adjustment for these variables, the EPO-RI was considered similar in both study groups. By study end, the temporal course of the power-transformed EPO-RI in both groups was identical, with a mean decline of 20%–25%, indicating that ESA responsiveness improved over time in both groups. Overall, the EPO-RI was not influenced by LC supplementation, even though the mean LC concentrations of the treatment group were five times higher than those in the placebo group. Achieving an EPO-RI >300 IU/kg per g hemoglobin was considered a hyporesponse. Six patients in the untreated group versus eight in the treatment group were hyporesponsive. In addition, no significant differences in plasma levels of LDL cholesterol or triglycerides between the two groups were discerned. This issue, with the underlying tenet that LC would favorably alter the dyslipidemic profile of patients with ESRD, had been previously studied (8). In addition, the frequency of intradialytic hypotension episodes did not differ between groups.

The lack of efficacy of LC in this study may relate to the "insufficiently low" levels of LC in the participants. Specifically, and ironically, the carnitine deficiency in the placebo group was insufficient to allow a determination of a positive effect of replacement therapy. This hypothesis would also explain why some trials have demonstrated a significant erythropoietic response to LC and why many clinicians, in their respective "*n* of 1" trials, have witnessed a salutary response when using LC as a last-ditch effort in their hyporesponsive patients who may have endured severe carnitine deficiency. In CARNIDIAL, the EPO-RI of the patients with the lowest free carnitine levels is not reported. Perhaps these patients actually responded positively to LC.

Finally, the water-soluble and dialyzable vitamin C/ascorbate is itself an antioxidant and a necessary component in the biosynthesis of LC. Ascorbate has been used concomitantly with LC in anemia trials. Perhaps some of the success regarding anemia treatment attributed to LC has actually derived from vitamin C administration. Congruent with this thesis is the report of Attallah and colleagues, who augmented an erythropoietic response in anemic hemodialysis patients with adjuvant vitamin C but without LC (24).

On balance, however, despite its putative effects, LC supplementation should not be considered part of the routine treatment of anemia in hemodialysis patients. Staples such as iron, rHuEPO and its related compounds in appropriate measure, dialytic adequacy, and all applicable measures to reduce inflammation continue to represent the safest and standardized therapeutic approach for the anemia of CKD. LC should be used to treat anemia only in dialysis patients with documented LC deficiency in whom all other conventional measures to raise hemoglobin have been attempted and failed.

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Disclosures

Jerry Yee serves on the advisory boards of Alexion, Amgen, Merck, and Reata and is editor-in-chief of *Advances in Chronic Kidney Disease* (National Kidney Foundation).

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