L-Carnitine Treatment of Anemia

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• **Recombinant human erythropoietin (rHuEPO) and iron supplementation have had a profoundly positive impact on the anemia of patients with chronic kidney disease. However, a significant number of patients remain hyporesponsive to rHuEPO, with hemoglobin values less than target levels. A suboptimal response to rHuEPO is associated with complications that can reduce quality of life and increase morbidity, mortality, and costs. There are a number of other metabolic derangements associated with uremia that can impact on the production and survival of red blood cells. Dialysis-related carnitine disorder is a functional metabolic deficiency, common in chronic dialysis patients, that can have a negative impact on erythrocyte production and survival. This article reviews the role of L-carnitine in the pathogenesis and adjunctive treatment of anemia associated with kidney failure. After a comprehensive database search, primary and secondary reports were analyzed. Laboratory studies examining the influence of carnitine on red blood cell function and clinical trials of L-carnitine in dialysis patients support the use of L-carnitine in the setting of rHuEPO hyporesponsiveness. Consensus groups, including the National Kidney Foundation-Kidney Disease Outcome Quality Initiative (K/DOQI), consider the use of L-carnitine for hyporesponsive rHuEPO-dependent anemia a promising application of this therapy, recommending an empiric trial of L-carnitine in these patients.** ***Am J Kidney Dis*** **41:S27-S34.**

INDEX WORDS: L-Carnitine; levocarnitine; carnitine; anemia; epoetin; epoetin resistance; dialysis; uremia; chronic renal failure (CRF); end-stage renal disease (ESRD); kidney failure.

ANEMIA IS A well-recognized complication of chronic kidney disease and end-stage renal disease (ESRD), resulting primarily from diminished erythropoietin production by diseased kidneys. Recombinant human erythropoietin (rHuEPO) is available for human use to supplant the endogenous deficiency of the hormone, but other factors may limit the ability of the bone marrow to respond to rHuEPO. The most common factor is iron deficiency,[1] but folate and vitamin B_{12} deficiency, severe secondary hyperparathyroidism, aluminum toxicity, inflammation, infection, surgery, and malignancy also may have a role in individual patients.[2-5] In addition, hemoglobinopathies, chronic blood loss (eg, at the hemodialysis [HD] procedure), and shortened red blood cell lifespan caused by hemolysis or hypersplenism can contribute to a lack of response to rHuEPO and the need for greater doses.[6]

The National Kidney Foundation (NKF)-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000 define an inadequate response to rHuEPO as failure to achieve or maintain the target hemoglobin level of 11 to 12 g/dL (110-120 g/L) or a hematocrit of 33% to 36% in the presence of adequate iron stores at a rHuEPO dose of 450 U/kg/wk intravenously (IV) or 300 U/kg/wk subcutaneously.[7] Data from the 2001 ESRD Clinical Performance Measures Project showed that 26% of patients had a mean hemoglobin value less than the target range.[8] Of these, 2% of patients had hemoglobin levels less than 9 g/dL (90 g/L) with a corresponding mean rHuEPO dose of 179 U/kg/dose (equivalent to 537 U/kg/wk IV for a typical patient). Such patients fit the K/DOQI criteria for rHuEPO hyporesponsiveness and would be ideal candidates for adjunctive therapy to support the target hemoglobin level.

A suboptimal response to rHuEPO is associated with many symptoms and physiological disorders that reduce quality of life, including reduced exercise tolerance, impaired cognition and mental acuity, anorexia, insomnia, and depression.[9,10] Anemia is an independent risk factor for the development of heart failure and a predictor of mortality in dialysis patients.[11] Furthermore, rHuEPO resistance has been associated

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with congestive heart failure and dialysis-related hypotension. Therapies that could improve hyporesponsive rHuEPO-dependent anemia thus would be beneficial. L-Carnitine therapy may be an effective treatment for these problems associated with anemia.[12-14]

Patients on chronic HD therapy are likely to have a dialysis-associated carnitine disorder (DCD) in which a secondary carnitine deficiency arises because of a combination of factors: inadequate intake, impaired renal synthesis of carnitine, and its efficient removal by HD. In addition to the absolute deficiency of L-carnitine encountered with a DCD, there is disruption of the normal ratio of free to acylcarnitines.[15] This report reviews the role of L-carnitine in the pathogenesis and treatment of anemia associated with chronic kidney failure.

L-CARNITINE AND ERYTHROCYTE FUNCTION

The main cellular function of carnitine is to facilitate the entry of long-chain fatty acids into mitochondria for oxidation and provision of energy in the form of adenosine triphosphate (ATP). Carnitine is required for the export of short-chain acyl residues out of mitochondria.[16,17] The salutary effects of L-carnitine on anemia center on improvement of erythrocyte survival, specifically through enhanced erythrocyte membrane stability.[18] An in vitro study showed that erythrocyte membrane stability had a biphasic response to L-carnitine, showing relative improvement in stability at physiological concentrations and a loss of stability at concentrations greater than 50 μmol/L of L-carnitine. Erythrocyte deformability (the ability to change shape while circulating through capillaries) was not affected in this study.[16] Furthermore, the addition of L-carnitine to the preservation solution of packed red blood cells reduced hemolysis during storage and increased subsequent in vivo survival of the transfused cells.[19]

Nicolaos et al[17] reported that after 3 months of 30 mg/kg of L-carnitine administered IV postdialysis, red blood cell deformability and hematocrit were significantly improved in 15 HD patients. In 26 HD patients, Matsumura et al[20] found a significant inverse correlation between serum total carnitine levels and both erythrocyte fragility and weekly maintenance rHuEPO doses. The investigators concluded that low serum carnitine levels accelerated erythrocyte osmotic fragility and negatively influenced the efficacy of rHuEPO. Another study confirmed the positive effects of L-carnitine, 3 mg/kg IV, postdialysis for 4 months on red blood cell membrane stability and hematocrit in 18 HD patients.[21] The investigators proposed that a reduction in rHuEPO dose and frequency of administration may be achieved by adding a low dose of L-carnitine.[21] Conversely, Kletzmayr et al[22] were unable to confirm an increase in erythrocyte survival time in a small number of L-carnitine–treated patients.

L-Carnitine stabilization of erythrocyte membranes may occur through several possible mechanisms. Labonia et al[23] observed that in eight patients, L-carnitine supplementation of 1 g/d orally plus 1 g/d IV postdialysis for 2 months increased hematocrit and enhanced cellular sodium, potassium adenosine triphosphatase (Na^+,K^+-ATPase) activity, thereby maintaining the biconcave discoid shape of erythrocytes. The proposed mechanism was an increase in fatty acid transport and oxidation by L-carnitine, thereby reducing plasma Na^+,K^+-ATPase inhibitors.

Similarly, Donatelli et al[24] reported improved hematocrits and a reduction in the abnormally high erythrocyte ATP concentrations after treatment of 10 HD patients with L-carnitine, 1 g orally twice daily for 2 months. Erythrocyte ATP levels are markedly elevated in uremic patients. Donatelli et al[24] suggested that L-carnitine treatment reverses the accumulation of long-chain acyl carnitine esters that inhibit membrane Na^+,K^+-ATPase and contribute to cell lysis.

A recent study by Agroyannis et al[25] found that uremic patients have greater erythrocyte calcium levels than control subjects without uremia. These abnormally high levels were reduced in HD patients treated with L-carnitine, 1 g/dialysis session IV, suggesting that L-carnitine also may preserve functional properties of the erythrocyte membrane by protecting erythrocytes from the toxicity of high intracellular calcium levels.

There are several additional cellular-based mechanisms that might explain the effect of L-carnitine on the erythropoietic process. rHuEPO resistance has been correlated with elevation of levels of inflammatory mediators, interleukin-6, tumor necrosis factor-α, and interferon-γ.[26] In addition, indicators of an acute-phase response,

such as elevated C-reactive protein levels and low serum transferrin levels, also predict rHuEPO responsiveness.[27-29] Others have reported that the inhibition mediated by interferon-γ was associated with increased ceramide levels in bone marrow cells.[30,31] Ceramide is an intracellular mediator of apoptosis and thus would be involved in the life spans of erythroid precursors or mature erythrocytes. Therefore, inflammatory cytokines and other humoral factors seem to be associated with rHuEPO resistance and decreased erythroid colony formation.

In addition to inflammatory markers, indices of enhanced lipid peroxidation have been linked to rHuEPO resistance. Gallucci et al[32] found a significant inverse relationship between red blood cell malondialdehyde level, a measure of lipid peroxidation processes, and hemoglobin and hematocrit levels achieved with rHuEPO therapy. Moreover, the ability to maintain a stable hemoglobin level after treatment with rHuEPO correlated with a lower level of lipid peroxidation in red blood cell membranes.[33]

The impact of L-carnitine on tumor necrosis factor-α, ceramide, and lipid peroxidation may help explain its positive effects on rHuEPO requirements and anemia correction. IV L-carnitine treatment led to a significant reduction in plasma malondialdehyde levels in a set of HD patients.[34] This is consistent with the decrease in lipid peroxidation associated with L-carnitine administration in a number of other conditions.[35-37] A decrease in ceramide production, an intracellular mediator of apoptosis by mononuclear cells, also has been associated with L-carnitine.[38,39] Together, this evidence supports the biological plausibility of the benefit of L-carnitine in rHuEPO-resistant anemia.

L-CARNITINE IN THE ANEMIA OF ESRD

Relationship of Carnitine Levels to Severity of Anemia

Kooistra et al[40] first described the relationship between L-carnitine and anemia. They noted that patients with severe anemia requiring rHuEPO had lower carnitine levels than patients who had less severe or no anemia. Furthermore, in 16 patients with stable hematocrits, maintenance rHuEPO doses correlated inversely with total serum carnitine levels ($r = -0.58$; $P < 0.05$; Fig 1).[40] In this study, there was no correlation between rHuEPO dose and free carnitine levels. However, Matsumura et al[20] showed a significant inverse correlation between the rHuEPO dose required to maintain target hematocrit and both total carnitine ($r = -0.54$; $P < 0.05$) and free carnitine levels ($r = -0.50$; $P < 0.05$) in serum. These data suggest that L-carnitine deficiency may contribute to the need for greater rHuEPO doses in patients with ESRD with anemia. Conversely, greater carnitine levels should lead to a reduction in rHuEPO requirements for the treatment of anemia in ESRD, a finding reported by Caruso et al.[41] However, this has not been corroborated in other studies that examined this question.[22,42]

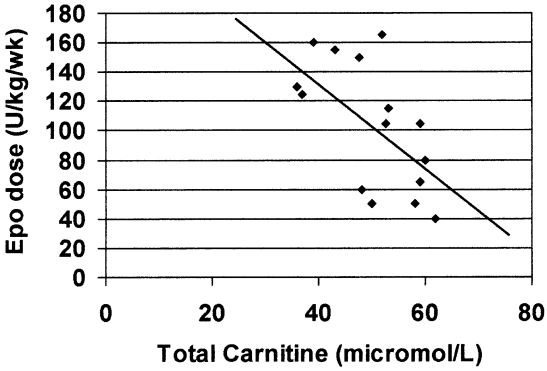

Fig 1. Erythropoietin (Epo) dose and plasma carnitine levels. $r = -0.58$; $P < 0.05$. (Reprinted with permission.[40])

Clinical Evidence for L-Carnitine Treatment of Anemia

L-Carnitine has been shown to increase hematocrits in non–rHuEPO-treated patients and reduce rHuEPO requirements in patients on maintenance rHuEPO therapy (Tables 1 and 2). Although few randomized controlled trials exist, there is convincing evidence for benefit from L-carnitine treatment in this setting. Studies conducted before the availability of rHuEPO focused on the efficacy of L-carnitine in correcting anemia in HD patients.[43,44] In a randomized placebo-controlled study, Trovato et al[43] reported an increase in mean hematocrit from 25.5% $\pm$ 1.4% to 37.4% $\pm$ 2.2% in 12 patients after 12 months of treatment with L-carnitine ($P < 0.001$). During the same period, hematocrits decreased in the placebo group.

Several randomized controlled studies also

Table 1. Randomized Controlled Trials on L-Carnitine Effects on Anemia in HD Patients

Reference Year	No. of Patients (treatment/control)	Double Blind	Route of Administration	L-Carnitine Dosage	Treatment Duration	Results	*P*
No rHuEPO treatment							
Trovato et al[43] 1982	13/13	No	Oral	0.8 g twice daily	52 wk	Hct and Hgb increased	<0.001
Bellinghieri et al[44] 1983	7/7	Yes	Oral	1 g twice daily	2 mon	Hct increased	<0.05
rHuEPO treatment							
Labonia[42] 1995	13/11	Yes	IV	1 g postdialysis	6 mon	rHuEPO dose decreased: T_0 = 102.2 ± 52.6 U/kg/wk; T_6 = 63.3 ± 37.8 U/kg/wk	<0.02
Caruso et al[41] 1998	15/16	Yes	IV	1 g postdialysis	6 mon	rHuEPO dose decreased in patients > 65; T_0 = 135 ± 79 U/kg/wk; T_6 = 118 ± 108 U/kg/wk; no change in group as a whole	
Kletzmayr et al[22] 1999	20/20	Yes	IV	5 & 25 mg/kg postdialysis	4 mon	rHuEPO dose decreased in 8/19 patients: T_0 = 183.7 ± 131.7 U/kg/wk; T_4 = 126.6 ± 127.9 U/k/wk; no change in rHuEPO dose for group as a whole, but ERI decreased ($P < 0.02$)	<0.001

Abbreviations: Hct, hematocrit; Hgb, hemoglobin; ERI, rHuEPO resistance index.

reported a beneficial effect of L-carnitine during rHuEPO therapy.[22,41,42] Labonia[42] showed a 38.1% reduction in rHuEPO dose from a mean of 102 ± 52.6 to 63.3 ± 37.8 U/kg/wk after 6 months of therapy with L-carnitine, 1 g IV postdialysis ($P < 0.02$), whereas there was no change in rHuEPO dose requirement in the placebo group. Of the 13 patients in the treatment group, 7 patients responded with a reduction in rHuEPO dosing requirement, whereas the others had no change. Responders had a tendency toward a greater mean rHuEPO requirement and greater endogenous erythropoietin levels at baseline. There was no correlation between serum carnitine level and response.

Two recent studies have attempted to further define the patient subpopulations most likely to benefit from L-carnitine treatment of anemia. Kletzmayr et al[22] reported a 36.9% rHuEPO dose reduction (from 183.7 ± 131.7 to 126.6 ± 127.9 U/kg/wk) in 8 of 19 patients treated with IV L-carnitine. However, when all levocarnitine-treated patients were considered together, there was no significant change in rHuEPO dose. Patients responding to L-carnitine therapy had greater total serum carnitine levels at baseline than nonresponders ($P < 0.05$); however, there was no correlation between individual rHuEPO requirement and carnitine level. Although L-carnitine at 25 mg/kg (but not 5 mg/kg) administered postdialysis increased serum carnitine levels into the reference range, the study was not able to show a clear advantage of low-dose or high-dose L-carnitine supplementation because of the small number of patients (n = 5) in the high-dose group.[22]

Table 2. Nonrandomized Studies and Reports on L-Carnitine Effects on Anemia in Hemodialysis Patients

Reference Year	No. of Patients (treatment/control)	Double Blind	Route of Administration	L-Carnitine Dose and Regimen	Treatment Duration	Results	*P*
No rHuEPO treatment							
Albertazzi et al[46] 1982	23	No	Oral or in dialysate	1 g or 100 μmol/L in dialysate	6 mon	Hct increased	<0.02
Vacha et al[45] 1983	29/12	Yes	IV	20 mg/kg postdialysis	4 mon	Hct increased	<0.001
Nilsson-Ehle et al[55] 1985	14/14	Yes	IV	2 g postdialysis	6 wk	No effect	NS
Donatelli et al[24] 1987	10/10	No	Oral	1 g twice daily	2 mon	Hct and Hgb increased	<0.02
rHuEPO treatment							
Berard and Iordache[47] 1992	2	No	IV	1–3 mg/kg postdialysis	9 mon	Hct increased	Not reported
Berard et al[21] 1994	18	No	IV	3 mg/kg postdialysis	4 mon	rHuEPO dose reduced or maintained	Not reported
Boran et al[48] 1996	14	No	IV	40–60 mg/kg/wk postdialysis	3 mon	Hct increased SC rHuEPO dose reduced; T_0 = 151 ± 21 U/kg/wk, T_3 = 87 ± 32 U/kg/wk	<0.0001
Kavadias et al[49] 1996	8	No	IV	2 g postdialysis	9 mon	rHuEPO dose reduced by > 50%; rHuEPO dose at T_0 = 150 to 180 U/kg/wk	Not reported
Trovato et al[50] 1998	25/35	No	IV, oral	1 g IV postdialysis and 1 g orally on nondialysis days	3 y	rHuEPO dose decreased: T_0 = 5971 ± 1732 U/wk, T_3 = 3391 ± 659 U/wk	<0.001
Simard et al[51] 1999	1	No	IV	2 g postdialysis	2 y	Hct increased	Not reported
Lilien et al[56] 2000	16 (children)	No	Oral	10 mg/kg twice daily	26 wk	No change in Hgb, Hct, or rHuEPO dose: T_0 = 191 ± 124 U/kg/wk, T_3 = 222 ± 659 U	NS
Nikolaos et al[17] 2000	15	No	IV	30 mg/kg postdialysis	3 mon	Hct increased with no change in rHuEPO dose	<0.0001
Kawabata et al[52] 2001	1	No	Oral	500 mg/d	7 mon	Hgb and Hct increased	Not reported
Matsumoto et al[53] 2001	14	No	Oral	500 mg/d	3 mon	Hct increased in 7/14 poor rHuEPO responders	0.003
Vesela et al[54] 2001	12/12	No	IV	15 mg/kg at dialysis	6 mon	rHuEPO dose decreased 37%: T_0 = 5500 U/wk, T_6 = 3500 U/wk	<0.001

Abbreviations: Hct, hematocrit; Hgb, hemoglobin; SC, subcutaneous; NS, not significant.

In a similar study of patients randomly assigned to treatment or placebo, Caruso et al[41] identified that elderly patients showed more benefit than younger patients from treatment with L-carnitine, 1 g IV postdialysis. Furthermore, the reduced rHuEPO dose requirements shown during treatment reverted toward baseline during the 3-month follow-up period when L-carnitine was withheld. However, when data from both the younger and older groups were combined, no benefit of L-carnitine was shown. Another study also noted that therapeutic effects were lost within a few weeks after discontinuation of L-carnitine therapy.[45]

Several other case reports and studies with less rigorous designs lend additional evidence for L-carnitine benefit.[17,21,24,45-54] However, two studies showed no benefit of L-carnitine on anemia-related parameters,[55,56] one of which involved iron-deficient pediatric patients.[56] Patients identified as having a poor response to rHuEPO have been specifically targeted for L-carnitine therapy.[47,52,53] Matsumoto et al[53] reported that L-carnitine, 500 mg/d orally, was associated with increased hematocrits in 7 of 14 patients with hyporesponsive rHuEPO-dependent anemia, whereas reports of individual cases of anemia improvement lend additional support.[47,52]

A meta-analysis of L-carnitine supplementation studies in HD patients was conducted by Hurot et al.[57] Randomized controlled trials of L-carnitine in anemia were found in the aggregate to show a promising effect of L-carnitine on anemia management. The investigators recommended a large, randomized, controlled trial to analyze the cost versus benefit of L-carnitine's potential rHuEPO dosage-sparing effect. In an editorial comment, Bommer[58] also discussed the probability of cost savings of reduced rHuEPO doses by administering L-carnitine. He concluded that L-carnitine may improve anemia and reduce rHuEPO requirements in a subgroup of HD patients.

Two groups of experts also evaluated the efficacy of L-carnitine in the treatment of anemia of ESRD. The 1994 American Association of Kidney Patients (AAKP) Consensus Group on the Role of Levocarnitine in Treating Renal Dialysis Patients conducted an extensive review of L-carnitine efficacy.[59] They concluded there is a definite role for L-carnitine in dialysis patients, particularly for certain conditions that do not adequately respond to standard therapy. These conditions include anemia unresponsive to or requiring large doses of rHuEPO (hyporesponsive rHuEPO-dependent anemia), muscle cramps, hypotension, lack of energy, skeletal muscle weakness, and cardiomyopathy. The AAKP Consensus Group noted that plasma carnitine levels have not been shown to be good predictors of the clinically effective carnitine dose. Although no optimum dose has been established, that group recommended a dose of L-carnitine of 20 mg/kg IV administered postdialysis.

More recently, the NKF-K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure[60] reported that the most promising of the proposed applications for L-carnitine in dialysis patients is in the treatment of rHuEPO-resistant anemia. They suggested that a 4-month trial of L-carnitine (~1 g after dialysis) was reasonable in selected patients with anemia and/or very large rHuEPO requirements (hyporesponsive rHuEPO-dependent anemia) and should be of adequate duration to reliably assess the response to L-carnitine.

In summary, L-carnitine has been shown to be effective in many patients for the adjunctive treatment of anemia associated with kidney disease. Studies of L-carnitine treatment of anemia have reported no adverse effects. In addition, this therapy has great potential for reduction of the significant costs associated with rHuEPO in some dialysis patients. At this time, experts recommend L-carnitine only for treatment of patients with hyporesponsive rHuEPO-dependent anemia. However, additional randomized controlled trials of sufficient power to clarify the mechanism of action and correlation of carnitine level with clinical efficacy may lead to an enhanced understanding of the beneficial effect of L-carnitine on anemia in maintenance dialysis patients in the future.

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