# L-Carnitine Effects on Anemia in Hemodialyzed Patients Treated With Erythropoietin

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● To demonstrate whether L-carnitine treatment could further improve the anemia in dialyzed patients under recombinant human erythropoietin (r-HuEPO) therapy, leading to a reduction in r-HuEPO requirements, L-carnitine (1 g intravenously after every dialysis session) was administered for 6 months to a group of 13 patients; the results were compared with data from a placebo control group (N = 11). Globular osmotic fragility and endogenous EPO secretion were also evaluated. L-Carnitine treatment promoted a 38.1% reduction in r-HuEPO requirements in the active group (102.2 ± 52.6 U/kg/wk *v* 63.3 ± 37.8 U/kg/wk; $P < 0.02$), with globular osmotic fragility and endogenous EPO levels remaining unchanged and thus not accounting for carnitine effect on anemia. In the active group, seven patients decreased r-HuEPO needs (responders), while six did not (nonresponders). Compared with nonresponders, responders showed higher mean values at time 0 for r-HuEPO requirements and endogenous plasma EPO levels, although not statistically significant. It is concluded that L-carnitine deficiency might promote EPO resistance in dialyzed patients, which is corrected by L-carnitine supplementation, ultimately reducing r-HuEPO requirements.



INDEX WORDS: L-Carnitine; anemia; hemodialysis; erythropoietin.

ANEMIA usually is present in patients with renal failure, often limiting their full rehabilitation. Several mechanisms have been involved as causal factors in the anemia of renal patients, including those that decrease erythropoiesis (eg, diminished erythropoietin [EPO] production,[1] iron, folate, and vitamin B12 deficiency,[2-4] aluminum toxicity,[5] hyperparathyroidism,[6,7] and the existence of circulating uremic inhibitors[8]) and those that decrease red blood cell half-life (eg, hemolysis[9] and hypersplenism[10]). It is now evident, however, that the most important factor causing renal anemia is the decrease in EPO secretion by the diseased kidney, having been clinically confirmed by the successful use of recombinant human EPO (r-HuEPO) in dialyzed patients in the last few years.[11-14]

Another causal factor that may contribute to the etiology of renal anemia is carnitine deficiency, which usually is observed in dialyzed patients.[15-18] In this sense, many investigators have demonstrated significant increases in hematocrit values after L-carnitine administration to renal patients undergoing hemodialysis, through yet unknown mechanisms of action.[19-23]

Kooistra et al recently showed that patients with anemia on chronic dialysis have lower serum carnitine levels than nonanemic renal patients; these investigators furthermore observed that renal patients with low carnitine levels seem to need higher doses of r-HuEPO.[24] In addition, Berard and Jordache also demonstrated that L-carnitine administration corrected r-HuEPO resistance in two hemodialyzed children.[25]

Accordingly, the present study aims to demonstrate whether L-carnitine supplementation to hemodialyzed patients under r-HuEPO maintenance treatment could further improve their hematologic status, also leading to a reduction in the r-HuEPO dose needed to achieve a desired hematocrit level. Globular osmotic fragility and endogenous EPO production were also determined to evaluate the underlying mechanisms responsible for L-carnitine effects on renal anemia.

## MATERIALS AND METHODS

### *Patients*

Twenty-four patients with end-stage renal disease of varying etiologies were studied. Inclusion criteria were as follows: on chronic hemodialysis for more than 1 year; dialysis frequency or duration unchanged for the previous 6 months; r-HuEPO treatment for a minimum of 6 months, with a defined maintenance dose, either intravenous or subcutaneous; hematocrit stable between 28% and 33% for the previous 3 months; normal iron status; usual treatment with folic acid and vitamin B12; no carnitine administration for the previous 6 months; and absence of severe clinical hyperparathyroidism. All the patients were stable and ambulatory, with no intercurrent diseases. None had received transfusions within the last 6

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*Received March 28, 1995; accepted in revised form June 27, 1995.*

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*0272-6386/95/2605-0008$3.00/0*

months. None were under angiotensin-converting enzyme inhibitor treatment. The patients were randomly assigned either to an active group or a placebo group. There were 13 patients in the active group (six men and seven women), their ages ranging from 25 to 71 years (mean age, 41.8 ± 18.6 years). The 13 patients in the active group had been receiving 4-hour, thrice-weekly intermittent hemodialysis for 13 to 174 months (mean, 80.4 ± 47.4 months) and r-HuEPO for 9 to 50 months (mean, 22.5 ± 11.6 months). There were 11 patients in the placebo group (five men and six women), their ages ranging from 54 to 76 years (mean age, 62.5 ± 7.2 years). The 11 patients in the placebo group had been receiving 4-hour, thrice-weekly hemodialysis for 13 to 140 months (mean, 50 ± 38.2 months) and r-HuEPO for 12 to 60 months (mean, 23.8 ± 14.8 months).

### *Study Design*

At time zero (T0), baseline determinations of various humoral parameters were carried out, including general laboratory measurements, complete hemogram, and iron status evaluation (ie, ferremia, serum transferrin, and ferritin). Globular osmotic fragility was also measured as a means of evaluating red blood cell membrane resistance to osmotic stress. Additionally, serum total and free carnitine levels were determined. Endogenous EPO levels in plasma were also measured at least 24 hours after the last intravenous r-HuEPO dose administered to the patient and at least 72 hours after the last subcutaneus r-HuEPO dose to avoid interferences with exogenous r-HuEPO, which is totally absent in plasma after such washout periods.[26] Following this scheme, endogenous EPO production (ie, EPO secreted by the patient's own kidneys) was evaluated.

After baseline determinations, either placebo (distilled water) or L-carnitine (Albicar, Laboratorios Casasco SAIC, Buenos Aires, Argentina; 1-g vials) at a dose of one vial intravenously after every dialysis session was initiated and continued for 6 months. When related to body weight, the mean carnitine postdialysis dose was 17.9 ± 2.8 mg/kg. Patients were randomly assigned to the placebo or carnitine group, and the study was conducted under double-blind conditions. A complete hemogram, including platelet and reticulocyte count, was performed every 2 weeks, while general laboratory measurements were repeated every month. Globular osmotic fragility, serum carnitine determinations, and serum EPO levels were also measured at T3 and T6 (months 3 and 6, respectively).

### *Recombinant Human Erythropoietin Posology Scheme*

The target hematocrit was 28% to 33% throughout the entire study. With hematocrit values greater than 28% at two consecutive determinations, r-HuEPO maintenance weekly dose was first reduced by 30% at T2. At T3, T4, and T5, r-HuEPO weekly dose was further reduced by 30% each time, with respect to the immediate previous dose, provided that the hematocrit level was 29% to 33% at two consecutive determinations. If hematocrit was 28%, r-HuEPO dose remained unchanged; with hematocrit less than 28%, r-HuEPO dose was increased by 30%.

### *Iron Status*

Serum iron, transferrin, and ferritin were measured every month and, considering that iron deficiency is the most common cause of acquired resistance to r-HuEPO,[12] patients were treated to maintain normal iron levels throughout the study, which were defined as follows: serum iron greater than 70 μg/dL, serum ferritin greater than 100 ng/mL, and serum transferrin saturation greater than 20%. Therefore, any deficiency was treated with either oral (ferrous sulfate 300 mg one to three times a day) or intravenous (iron dextran 100 mg two to three times per week) iron supplementation, the administration route depending on efficacy and gastric tolerance. Throughout the entire study, blood samples were obtained after a 12-hour fasting period just before dialysis.

### *Methods*

Globular osmotic fragility was measured at T0, T3, and T6 by means of a quantitative method without inhibition using 0.10% to 0.85% NaCl with final lecture at 530 mμ; normal values for 50% hemolysis were 0.40% to 0.445% NaCl for this method (medium corpuscular fragility).

Plasma EPO levels were measured by radioimmunoassay, while plasma carnitine was determined using the classical method described by McGarry and Foster, as modified by DiMauro.[27] Normal values for plasma total and free carnitine and the free/total ratio were, respectively, 45 to 75 μmol/L, 40 to 60 μmol/L, and 80% to 90%.

Hemograms were obtained through a cellular counter (Cell-Dyn; Abbott, Chicago, IL), transferrin by radial immunodiffusion with Behring-Werke plaques (Marburg, Germany), and ferritin by the microparticles enzyme immunoassay (MEIA) method using an IMX (Abbott).

### *Hemodialysis*

All patients underwent 4-hour hemodialysis sessions thrice weekly using Baxter CF-23 filters (Deerfield, IL), blood flow rates of 300 mL/min, dialysate flow rates of 500 mL/min, continuous heparinization with a mean total dose of 8,000 IU, and acetate as dialytic buffer. Dialyzers were reused with 4% formaldehyde as sterilant, manually reprocessed, and discarded whenever the blood compartment volume was less than 80% of the original volume.

### *Statistical Analysis*

Student's *t*-test was used to evaluate statistical significance. The various correlations were evaluated by linear regression (Pearson's *r*). All results are expressed as mean ± SD.

## RESULTS

Recombinant human erythropoietin dose, globular osmotic fragility, endogenous EPO, and carnitine levels are outlined in Table 1.

### *Recombinant Human Erythropoietin Dose*

In the carnitine-treated group, the mean weekly dose of r-HuEPO was 5,615.4 ± 2,631.2 U/wk at T0; at the end of the study (T6), the

**Table 1. Recombinant Human Erythropoietin Dose, Globular Osmotic Fragility, Plasma Erythropoietin, and Carnitine Levels in Carnitine and Placebo Groups at the Beginning (T0) and End (T6) of the Study**

| | Carnitine | | Placebo | |
|---|---|---|---|---|
| | T0 | T6 | T0 | T6 |
| rHuEPO dose | | | | |
| U/wk | 5,615.4 ± 2,631.2 | 3,538.5 ± 1,898* | 4,909.1 ± 2,314.2 | 4,909.1 ± 2,968.1 |
| U/kg/wk | 102.2 ± 52.6 | 63.3 ± 37.8* | 78.6 ± 32.1 | 79.9 ± 46.7 |
| Plasma carnitine (μmol/L) | | | | |
| Total | 69.9 ± 11.4 | 394.6 ± 124.2† | 62.9 ± 18 | 71.7 ± 13.1 |
| Free | 41.8 ± 7.1 | 247.7 ± 81.5† | 36.3 ± 9.7 | 47 ± 11.3 |
| Free/total (%) | 60 ± 7.7 | 61.6 ± 5.7 | 58.3 ± 6.6 | 64.6 ± 6.9 |
| Globular osmotic fragility (% NaCl) | 0.447 ± 0.031 | 0.452 ± 0.015 | 0.460 ± 0.015 | 0.453 ± 0.013 |
| Plasma EPO (mU/mL) | 33.1 ± 11.4 | 29.9 ± 15.2 | 40.1 ± 14.9 | 32.8 ± 13.4 |

*$P < 0.02$ (T0 *v* T6).
†$P < 0.001$ (T0 *v* T6).

mean dose was 3,538.5 ± 1,898 U/wk, a 37% reduction in the total r-HuEPO requirements ($P < 0.02$). When related to body weight, the mean r-HuEPO weekly dose for the active group was 102.2 ± 52.6 U/kg/wk at T0 and 63.3 ± 37.8 U/kg/wk at T6, representing a 38.1% reduction in the total r-HuEPO requirements ($P < 0.02$) (Fig 1).

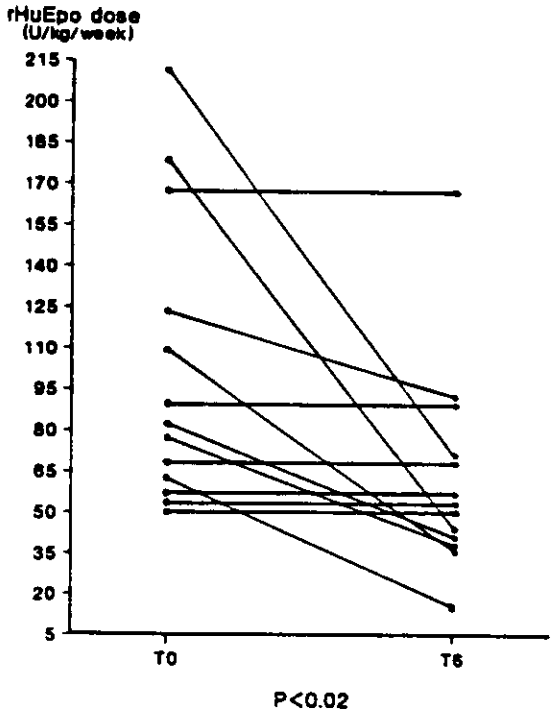


**Fig 1. Values for r-HuEPO requirements in the active group before (T0) and after 6 months (T6) of L-carnitine administration.**

In the placebo group, the mean weekly dose of r-HuEPO was 4,909.1 ± 2,314.2 U/wk at T0 and 4,909.1 ± 2,968.1 U/wk at T6, showing no significant reduction in r-HuEPO requirements ($P$ = NS). When related to body weight, the mean r-HuEPO weekly dose for the placebo group was 78.6 ± 32.1 U/kg/wk at T0 and 79.9 ± 46.7 U/kg/wk at T6, with no significant variation ($P$ = NS) (Fig 2).

No statistically significant differences were obtained when the mean values for the r-HuEPO weekly dose at T0 (both U/wk and U/kg/wk) in the active group were compared with mean values for the placebo group (Table 1).

*Hematocrit*

In the carnitine-treated group, the mean value for hematocrit was 29.8% ± 2.6% at T0 and 29.1% ± 2.1% at T6 ($P$ = NS). In the placebo group, the mean hematocrit value was 29.5% ± 2.3% at T0 and 27.9% ± 1.9% at T6 ($P < 0.05$) (Table 2).

As seen in previous data, although a reduction in r-HuEPO weekly dose was observed in four patients from the placebo group, it is noteworthy that a parallel decrease in hematocrit was also observed in these patients, accounting for the overall reduction in the mean hematocrit value for the whole placebo group (Fig 2).

*L-Carnitine Levels*

In the active group, mean values at T0 for total and free carnitine in plasma and the free/total ratio were, respectively, 69.9 ± 11.4 μmol/L,

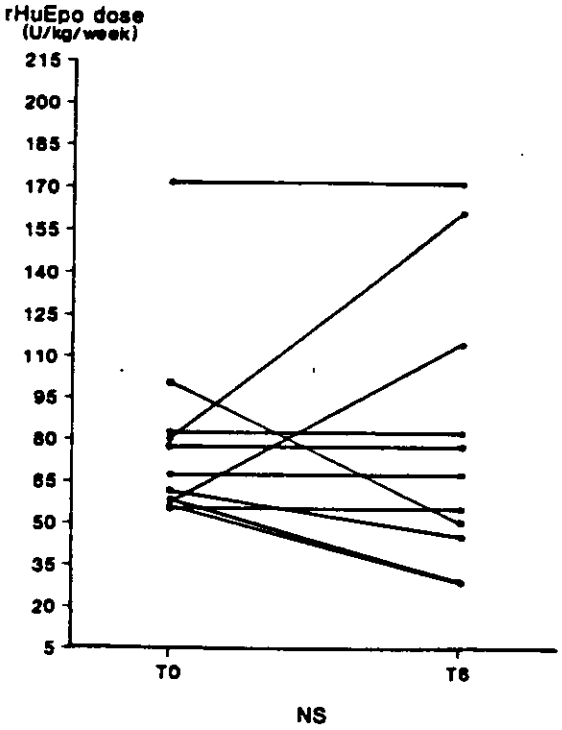


**Fig 2. Values for r-HuEPO requirements in the placebo group at the beginning (T0) and the end (T6) of the study.**

41.8 ± 7.1 μmol/L, and 60% ± 7.7%, while at T6 the mean values were, respectively, 394.6 ± 124.2 μmol/L, 247.7 ± 81.5 μmol/L, and 61.6 ± 5.7% (Table 1). Differences in total carnitine levels at T0 versus T6 were highly significant ($P < 0.001$), as were the free carnitine levels at T0 versus T6 ($P < 0.001$), representing a sixfold increment in both cases; however, the free/total carnitine ratio at T0 versus T6 remained unchanged ($P$ = NS) (Table 1).

In the placebo group, mean values at T0 for total and free carnitine and the free/total ratio were, respectively, 62.9 ± 18 μmol/L, 36.3 ± 9.7 μmol/L, and 58.3% ± 6.6%; at T6 the mean values were, respectively, 71.7 ± 13.1 μmol/L, 47 ± 11.3 μmol/L, and 64.6% ± 6.9%. Differences in T0 versus the corresponding T6 values were not significant ($P$ = NS) (Table 1).

*Globular Osmotic Fragility*

L-Carnitine administration did not modify globular osmotic fragility in the treated patients when values for T0 versus T6 were compared (0.447% ± 0.031% *v* 0.452% ± 0.015% NaCl; $P$ = NS) (Fig 3). Accordingly, no significant differences were found in globular osmotic fragility at T0 versus T6 in the placebo group (0.460% ± 0.015% *v* 0.453% ± 0.013% NaCl; $P$ = NS) (Table 1).

*Endogenous Erythropoietin Levels*

The mean value for endogenous plasma EPO levels at T0 in the active group was 33.1 ± 11.4 mU/mL, and L-carnitine administration failed to modify these levels when measured at T6 (29.9 ± 15.2 mU/mL; $P$ = NS) (Fig 4). Accordingly, no significant differences were found in endogenous plasma EPO levels at T0 versus T6 in the placebo group (40.1 ± 14.9 mU/mL *v* 32.8 ± 13.4 mU/mL; $P$ = NS). Comparing values in carnitine versus placebo patients, no significant differences were found (Table 1).

*Iron Requirements*

In the active group, seven patients required 300 mg/d of oral ferrous sulfate, while three patients required 600 mg/d of this compound. All these patients received the same iron dose scheme from T0 to T6, with no changes during the study. One patient required no iron supplementation at all, and two patients were shifted at T2 from 300 mg/d of oral ferrous sulfate to 300 mg/wk of intravenous iron dextran. Interestingly, these two patients showed no reduction in their r-HuEPO needs at the end of the study.

In the active group, the mean value for serum ferritin was 232.1 ± 114 ng/mL at T0 and 221 ± 79.4 ng/mL at T6 ($P$ = NS). In the placebo group, five patients required 300 mg/d and four required 600 mg/d of oral ferrous sulfate, while two patients received 200 mg/wk of intravenous iron dextran. All these patients received the same iron dose scheme from T0 to T6, with no changes throughout the study. In this group, the mean value for serum ferritin was 291.8 ± 206.4 ng/mL at T0 and 324.7 ± 215.7 ng/mL at T6 ($P$ = NS).

*Responders and Nonresponders*

After L-carnitine treatment, seven patients from the active group showed a marked decrease in their r-HuEPO requirements (responders), while six patients showed no change in their r-HuEPO needs (nonresponders). Using statistical

**Table 2. Laboratory Parameters in Carnitine and Placebo Groups at the Beginning (T0) and End (T6) of the Study**

| | Carnitine | | Placebo | |
|---|---|---|---|---|
| | T0 | T6 | T0 | T6 |
| Hematocrit (%) | 29.8 ± 2.6 | 29.1 ± 2.1 | 29.5 ± 2.3 | 27.9 ± 1.9* |
| Urea (mg/dL) | 176.1 ± 45.6 | 142.1 ± 34.8 | 166.4 ± 46.1 | 150.9 ± 56.1 |
| Creatinine (mg/dL) | 11.8 ± 2.1 | 10.9 ± 3.4 | 10.8 ± 1.9 | 10.3 ± 2.5 |
| Na (mEq/L) | 141.5 ± 3.3 | 143.1 ± 1.8 | 141 ± 2.7 | 143.2 ± 1.8 |
| K (mEq/L) | 5.9 ± 0.5 | 5.6 ± 0.4 | 5.8 ± 0.6 | 5.8 ± 0.3 |
| Ca (mg/dL) | 8.5 ± 0.7 | 9.6 ± 0.8 | 8.4 ± 0.5 | 9.3 ± 1.3 |
| Phosphate (mg/dL) | 6.6 ± 1.4 | 6.3 ± 1.5 | 6.2 ± 1.4 | 5.7 ± 1.5 |
| Total cholesterol (mg/dL) | 160.9 ± 26.2 | 144.1 ± 27.5 | 173.8 ± 35.5 | 164.5 ± 29.9 |
| HDL cholesterol (mg/dL) | 30.7 ± 8.9 | 38.5 ± 10.4 | 34.9 ± 11.6 | 43 ± 13.9 |
| Triglycerides (mg/dL) | 122.5 ± 50.1 | 106.8 ± 45.4 | 122 ± 53.8 | 138.5 ± 61 |
| Iron (μg/dL) | 88.7 ± 27.3 | 116 ± 39.1 | 91.7 ± 33.5 | 120.8 ± 32 |
| Iron-binding capacity (μg/dL) | 239.5 ± 93.7 | 260.5 ± 108 | 228.1 ± 64.2 | 275.4 ± 104.3 |
| Ferritin (ng/mL) | 232.1 ± 114 | 221 ± 79.4 | 291.8 ± 206.4 | 324.7 ± 215.7 |

Abbreviation: HDL, high-density lipoprotein.
*$P < 0.05$ (T0 *v* T6).

analysis, no correlations were found with age, body weight, dialytic age, dialysis efficacy (Kt/V), general laboratory parameters, globular osmotic fragility, plasma carnitine levels, carnitine dose per kilogram of body weight, or hematocrit. Etiologic factors, medications, and personal medical history also were evaluated, but no significant differences were found. In this regard, although the responders showed a mean value for r-HuEPO requirements at T0 that was higher than the mean value in nonresponders (120.3 ± 51.3 U/kg/wk *v* 81.2 ± 40.4 U/kg/wk; $P$ = NS), this difference was not statistically significant. Accordingly, similar differences were obtained for endogenous plasma EPO levels at T0, showing that the responders had a higher mean value than the nonresponders (38.6 ± 11.8 mU/mL *v* 26.8 ± 7 mU/mL; $P$ = NS), but this difference was also statistically nonsignificant. In both cases, the absence of statistically significant differences was probably due to the small size of the samples involved. Interestingly, in the responder group, five patients attained their lowest r-HuEPO requirement at T4, while the other two attained it at T3, suggesting that the maximum carnitine effect might be obtained in less than 6 months.

*General Measurements*

No significant differences were observed in the general laboratory parameters evaluated, neither in carnitine-treated patients at T0 versus T6 nor in the active group versus the placebo group (Table 2). In addition, no statistical differences were observed in the quality of dialysis treatment, assessed through Kt/V measurements, neither in the carnitine-treated patients at T0 versus T6 nor in the active group versus the placebo group.

## DISCUSSION

The anemia of chronic renal failure presents a multifactorial etiology, although the decrease in EPO production by the diseased kidney is regarded as the most crucial cause. In the last few years, a strong body of clinical evidence has confirmed the importance of r-HuEPO therapy in correcting renal anemia.[11-14,28] In normal conditions, the kidney is the major producer of EPO in adults[29] and the decrease in oxygen flow to renal tissue, occurring in patients with anemia, promotes a marked increase in EPO secretion, so that at hematocrits of 20% the plasma level of EPO is more than 100-fold higher than basal values.[30] In end-stage renal disease, a relative deficiency of EPO is commonly observed, because EPO plasma levels are usually in the normal range (10 to 30 mU/mL),[31,32] but are inappropriatelly low for the existent degree of anemia.[1,2] With regard to the final target of EPO, it is known that this hormone stimulates the maturation and

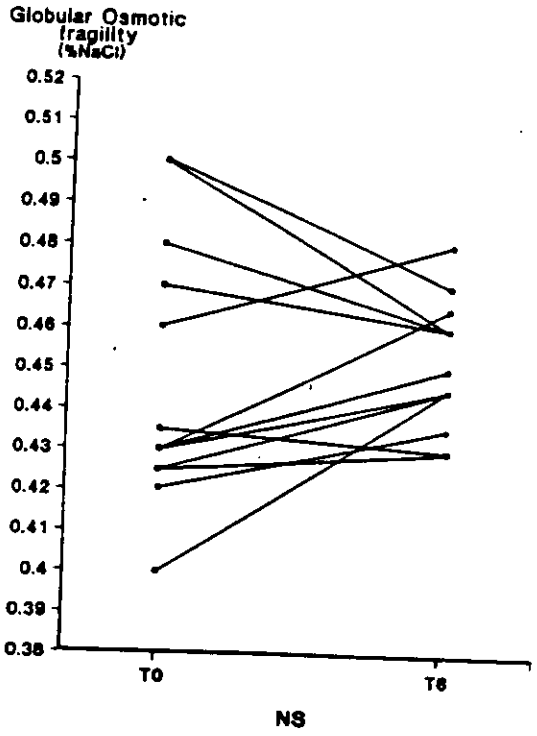


**Fig 3. Values for globular osmotic fragility in the active group before (T0) and after 6 months (T6) of L-carnitine administration.**

proliferation of erythroid precursors in bone marrow, mainly at the level of the colony-forming units–erythroid.[33,34]

Another causal factor that may play a role in renal anemia is carnitine deficiency. L-Carnitine (L-3-hydroxy-4-*N*-trimethylaminobutyric acid) is the natural carrier of fatty acids from the cellular cytoplasm to the mitochondrial matrix, where they undergo $\beta$-oxidation.[35] It has been classically stated that patients on chronic hemodialysis usually present severe carnitine deficiency due to a combination of inadequate intake, impaired synthesis, and excessive loss during dialysis.[15,16,36] The typical carnitine profile in patients on chronic dialysis, as compared with the normal population, shows lower free and normal total carnitine plasma levels, with lower free/total carnitine ratios and decreased muscle stores, despite normal total plasma levels.[37-39] Remarkably, the low free/total carnitine ratio reflects a relative or absolute increase in acyl-carnitine levels. With regard to renal anemia, many investigators have observed an increase in hematocrit after L-carnitine administration to patients on chronic dialysis due to causes that remain unclear.[19-21]

In theory, L-carnitine could modify the lipid composition of the red blood cell membrane,[21] thus increasing its resistance to different types of stress, which could eventually improve the erythrocyte half-life by decreasing hemolysis. In this study, globular osmotic fragility was measured as to evaluate this hypothesis. In addition, provided that one of the functions of carnitine in uremia, as in organic acidemias, might be to act as an intracellular "scavenger system," which traps and removes potentially toxic acyl groups, the acyl carnitine increase in uremia may suggest an impairment in fatty acid oxidation, thus yielding acyl residues that could promote metabolic derangements, ultimately leading to clinical disturbances, such as anemia.[40-42]

In the present study, L-carnitine administration promoted a 38.1% reduction in r-HuEPO requirements, whereas the target hematocrit remained unchanged. This beneficial effect of L-carnitine was due neither to an increase in red blood cell

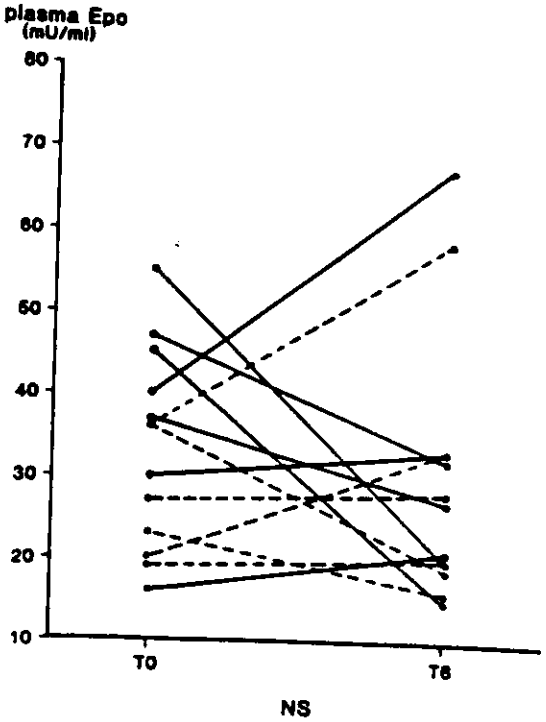


**Fig 4. Values for endogenous plasma EPO levels in the active group before (T0) and after 6 months (T6) of L-carnitine administration, comparing responders (solid lines) to nonresponders (broken lines).**

membrane resistance (as evaluated by globular osmotic fragility) nor to a higher secretion of endogenous EPO by the patients' kidneys. In this sense, it has been recently suggested that the erythrocytosis observed in some renal transplant recipients could be due to an increased EPO production by the diseased native kidneys,[43-45] thus demonstrating in patients with terminal kidney failure a renal reserve in terms of EPO synthesis, which, we hypothesized, could be stimulated by L-carnitine administration. We can speculate that L-carnitine improves renal anemia through its action on erythroid precursors, probably enhancing the stimulatory effects of EPO. Interestingly, in this study patients who responded to carnitine therapy showed higher mean values for r-HuEPO requirements at T0 as well as for endogenous EPO levels compared with nonresponders, although both results proved to be not statistically significant. Should these results be observed in a study involving a higher number of patients, the existence of EPO resistance caused by carnitine deficiency, and its reversal through carnitine supplementation, could be hypothesized.

In our study, all the patients presented a decrease in plasma-free carnitine and free/total ratio at T0, with normal values for total carnitine, in agreement with previous literature.[37-39] Nevertheless, the beneficial effect of carnitine supplementation could be related to the repletion of carnitine tissue stores, which were not evaluated in this study. Accordingly, we may hypothesize that the marked increase in free carnitine levels following carnitine supplementation might correct any derangement in fatty acid oxidation, due to carnitine deficiency, thus removing toxic acyl residues that could eventually disturb erythropoiesis.

## CONCLUSION

L-Carnitine treatment promoted a marked reduction in r-HuEPO requirements, which was related neither to higher endogenous EPO secretion by the patients' kidneys nor to any improvement in red blood cell membrane resistance. A hypothetical relationship between carnitine deficiency and EPO resistance may be suggested.

Although the number of patients under study was hardly enough to draw any definitive statements, it can be concluded that L-carnitine supplementation to patients undergoing chronic hemodialysis might reduce r-HuEPO requirements, thus approaching a more physiologic therapy profile and, additionally, lowering the cost of dialytic treatment.

## ACKNOWLEDGMENT

The author thanks Dr Pablo Rendo from BioSidus SA, Buenos Aires, Argentina, for the plasma EPO determinations, and Dr Leonardo Sivak for his practical assistance. L-carnitine was kindly provided by Laboratorios Casasco SAIC, Buenos Aires, Argentina.

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