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LONG-TERM L-CARNITINE TREATMENT OF CHRONIC ANAEMIA OF PATIENTS WITH END-STAGE RENAL FAILURE

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ABSTRACT

A randomized double-blind long-term study on the effect of L-carnitine on severe anaemia of 24 maintenance haemodialysis patients was performed for one year. Patients were divided into two groups: controls (inert placebo), treated patients (L-carnitine 1.6 g p.o. daily).

A significant increase in haematocrit, haemoglobin, red cell count and mean corpuscular haemoglobin concentration was observed; in comparison with the control group, an early improvement could be detected from the 3rd month, with further increases in the successive months of treatment.

There was no modification in serum iron and transferrin.

These favourable effects of long-term carnitine treatment on anaemia of maintenance haemodialysis patients could be related to an increasing uptake of structural lipids in impaired erythropoiesis of patients with carnitine deficiency.

No side effect attributable to carnitine was observed.

INTRODUCTION

Anaemia of chronic renal failure and, specially, of patients on long-term maintenance haemodialysis is commonly attributed to a lack of erythropoietic-stimulating-factor (ESF) or, more recently, of a renal erythropoietic factor (REF).[1,2] REF appears to be an enzyme system that, analogously to the renin-angiotensin system, cleaves part of a blood circulating substrate generating an active substance that is the functional erythropoietin.[3] This defect is often associated with slight or severe unresponsiveness of the bone-marrow to ESF, due to uraemia-related

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toxic substances and/or to an as yet undefined deficiency.

Haemolysis, possibly and mainly related to sublethal erythrocyte injury during haemodialysis, could also be implicated.[4-8] However, mechanical trauma during haemodialysis procedures may induce more or less severe cell-wall injury which eventually leads to haemolysis.

Lipid and phospholipid components of erythrocyte membrane may also be primarily altered by uraemia.[9]

Uraemic patients often show a carnitine depletion,[10] a condition that can be severely worsened by haemodialysis.

Carnitine is essential for the intramitochondrial transfer and oxidation of fatty acids; a beneficial effect is suggested on myocardial and skeletal muscle cells, and a relevant symptomatic improvement on asthenia and cramps is often observed in haemodialysis patients treated with carnitine.[11,12]

We examined the therapeutic effects of carnitine on the degree of anaemia of long-term maintenance haemodialysis patients.

PATIENTS AND METHODS

Twenty-six patients, 13 males and 13 females, 22 to 68 years old (average 47.54 ± 13.16) on maintenance haemodialysis, 4 or 5 hours 3 or 4 times a week for 2 to 12 years (mean 6.54 ± 3.86) were selected for the study. Two were anephric, and the others had negligible renal function with creatinine clearances of less than 2.0 ml/min.

Patients were randomly assigned to two groups of 13 subjects each and age and sex matched.

One group received 1.65 g/p.o. (= 5 ml) of L-carnitine* daily in two administrations (= 2.5 ml). The second group (controls) was given an inert placebo. The trial design was single-blind.

At the end of dialysis all the patients received intravenously:
Vitamin B12 = 2500 mcg,
Folic acid = 0.70 mg,
Vitamin PP = 12 mg,
Vitamin C = 150 mg,
Sodium ferrigluconate = 10 mg.

Coulter-Counter S Model red blood cells evaluation (haematocrit, red cell count millions/mm^3, haemoglobin g/dl, mean corpuscular volume/μ^3, mean corpuscular haemoglobin content pg, mean corpuscular haemoglobin concentration (g/dl), reticulocytes count, serum iron (ng/dl) and serum transferrin (mg/dl) were assessed twice a month.

Patients that required blood transfusion were not considered for data analysis.

Data analysis was performed by the unpaired Student's *t* test, comparing the two groups at three-month intervals; moreover unpaired Student's *t* test was performed between each period vs baseline values.

Data are expressed as mean ± 1 standard deviation.

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* L-carnitine drops (20-ml 30% bottles) were kindly supplied by Sigma-Tau S.p.A., Pomezia (Rome), Italy.

RESULTS

Two patients in the placebo group were excluded since they were put on blood transfusion for worsening of the anaemia.

Overall results are shown in Tables I and II. A significant increase in the haematocrit, red cell counts, haemoglobin and in mean corpuscular haemoglobin concentration was observed after 6, 9, and 12 months in

Table I — *Haematological results in control group (placebo)*

	Base	After 3 months	After 6 months	After 9 months	After 12 months
Haematocrit ml/dl	24.0 ± 3.58	21.88 ± 3.37	22.23 ± 3.29	21.19 ± 3.03	21.84 ± 3.16
Red cell count millions/mm^3	2.78 ± 0.41	2.59 ± 0.38	2.60 ± 0.37	2.36 ± 0.34	2.46 ± 0.36
Haemoglobin g/100 ml	8.34 ± 0.49	7.44 ± 0.37	7.41 ± 0.74	7.12 ± 1.24	2.46 ± 1.01
Mean corpuscular volume μ^3	89.75 ± 12.84	90.42 ± 12.67	90.27 ± 13.53	90.72 ± 17.00	90.28 ± 15.17
Mean corpuscular haemoglobin content %	26.38 ± 1.089	26.01 ± 0.76	25.46 ± 1.95	25.80 ± 5.39	26.33 ± 3.71
Mean corpuscular haemoglobin concentration g/dl	29.41 ± 0.85	28.77 ± 0.61	28.21 ± 1.40	28.44 ± 3.17	29.16 ± 2.36
Reticulocytes % of red cells	0.51 ± 0.12	0.63 ± 0.08	0.72 ± 0.09	0.44 ± 0.10	0.53 ± 0.07
Iron, serum µg/dl	45.6 ± 28.7	53.8 ± 15.2	48.7 ± 14.7	56.8 ± 13.2	53.2 ± 18.7
Transferrin mg/dl	284.7 ± 40.6	244.5 ± 51.2	243.9 ± 47.2	280.7 ± 57.3	264.3 ± 60.2

Table II — *Haematological results in carnitine-treated patients*

	Base	After 3 months	After 6 months	After 9 months	After 12 months
Haematocrit ml/dl	25.53 ± 1.43	27.84 ± 1.15	29.92 ± 1.34*	33.69 ± 1.81**	37.38 ± 2.24***
Red cell count millions/mm^3	2.92 ± 0.16	3.05 ± 0.13	3.36 ± 0.15*	3.80 ± 0.19**	4.10 ± 0.28**
Haemoglobin g/100 ml	7.01 ± 0.74	8.04 ± 0.69	9.07 ± 0.86	10.68 ± 0.18**	12.25 ± 0.44***
Mean corpuscular volume μ^3	90.53 ± 13.58	89.84 ± 13.54	89.31 ± 14.29	88.66 ± 11.91	87.95 ± 11.11
Mean corpuscular haemoglobin content %	24.86 ± 1.9	25.94 ± 1.77	27.07 ± 2.53	28.11 ± 0.33	28.82 ± 0.60
Mean corpuscular haemoglobin concentration g/dl	27.46 ± 1.43	28.87 ± 1.31	30.31 ± 1.77	31.7 ± 0.27	32.77 ± 0.54*
Reticulocytes % of red cells	0.44 ± 0.06	0.53 ± 0.04	0.48 ± 0.09	0.56 ± 0.04	0.48 ± 0.10
Iron, serum µg/dl	50.3 ± 11.2	42.7 ± 18.7	50.8 ± 22.5	46.3 ± 18.6	57.2 ± 15.8
Transferrin mg/dl	258.3 ± 60.9	263.5 ± 61.3	245.8 ± 37.5	270.9 ± 39.1	256.7 ± 37.8

* : $p < 0.05$
** : $p < 0.01$
*** : $p < 0.001$

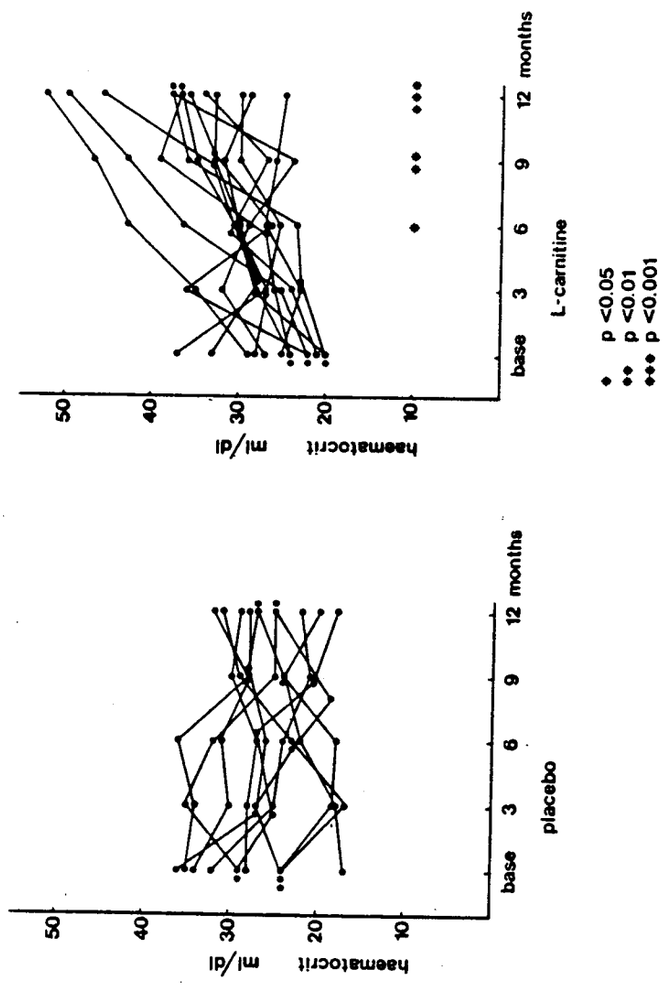


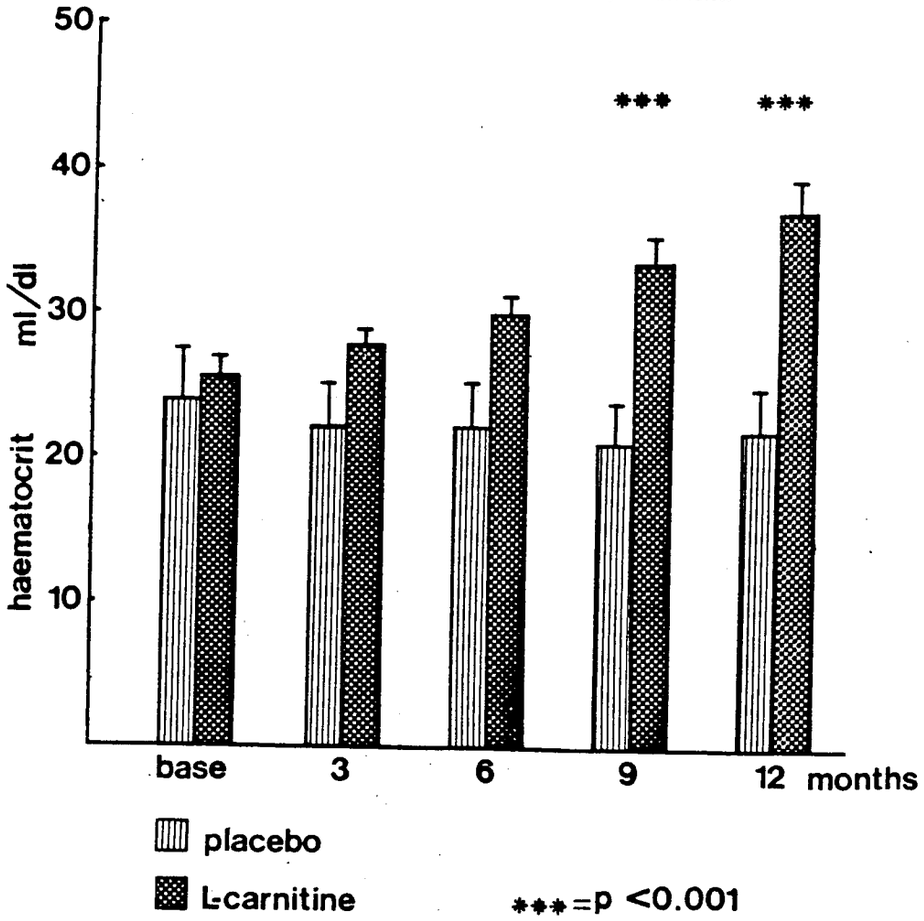
Figure 1 — *Haematocrit in carnitine-treated patients (right), and in the control group. A statistically significant increase (vs baseline) was observed from the 6th month of treatment in the carnitine group.*

the carnitine-treated group. No significant modification was observed in the reticulocyte count and in the serum iron and transferrin concentration.

In Figure 1 is shown the behaviour of the haematocrits in patients treated with carnitine or placebo. A significant improvement, as assessed by the paired Student's *t* test, was observed at the 6th, 9th and 12th month only in the carnitine group. As early as the 9th and 12th month a significant improvement in the haematocrit of the carnitine-treated group vs placebo was observed (Fig. 2).

Carnitine did not produce any side effect.

Figure 2 — *Haematocrit (mean ± SD) in carnitine-treated patients, and in the control group. A significant improvement in the treated versus placebo group was observed from the 9th month of treatment.*



The standard treatment of the patients and the haemodialysis methodology remained unchanged throughout the 12 months of the study.

DISCUSSION

Carnitine depletion in long-term haemodialysis is a well-known condition[10] and exogenous administration of the substance restores the blood and tissue deficiency.[13]

Given that decreased REF is the main cause of the anaemia exhibited by haemodialysed patients, we are not able — at present — to state that L-carnitine increased erythropoiesis. On the other hand, two observations — i.e. the stable blood reticulocyte levels and the gradual increase in haematocrit — leads us to give a different interpretation.

To account for significantly improved severe anaemia observed in our patients, we suggest that exogenous L-carnitine increases cholesterol and phospholipid uptake in the erythrocyte membranes and their metabolism, and therefore it is possible that carnitine improves survival of erythrocytes interfering with the membrane defect mechanisms of these patients. Experimental[14] and clinical trials[15,16] have in fact demonstrated that L-carnitine increases HDL-cholesterol and HDL transporters of structural lipids.

Despite some encouraging results in this type of patient treated with testosterone and other androgen drugs in individual dialysis patients, the danger of hepatic injury and of endocrine disturbances are a major contraindication.[17-19]

It can be suggested that L-carnitine — on contrast to long-chain esters thereof[20-22] — has an indirect membrane-stabilizing effect on carnitine-deficient patients.

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Key Words:

Haemodialysis, L-carnitine, anaemia.