Angina pectoris

Cacciatore L, Cerio R, Ciarimboli M, Cocozza M, Coto V, D'Alessandro A, D'Alessandro L, Grattarola G, Imparato L, Lingetti M.
The therapeutic effect of L-carnitine in patients with exercise-induced stable angina: a controlled study.
Drugs Exp Clin Res 1991;17(4):225-35
An investigation on the therapeutic effect of L-carnitine was performed at three different centres and included two hundred patients, 40 to 65 years of age, with exercise-induced stable angina. In one hundred randomly selected patients the drug was administered orally in daily doses of 2 g in addition to the already instituted therapy, and the effect studied over a 6-month period. Compared with the control group, these patients showed a significant reduction in the number of premature ventricular contractions (PVC) at rest, as well as an increased tolerance during ergometric cycle exercise as demonstrated by an increased maximal cardiac frequency, increased maximal systolic arterial blood pressure and therefore also increased double cardiac product and reduced ST-segment depression during maximal effort. This was accompanied by improvement in cardiac function and resultant performance, as shown by an increase in the number of patients belonging to class I of the NYHA classification and a reduction in the consumption of cardioactive drugs. Laboratory analysis showed an improvement in plasma lipid levels. The authors conclude, after having discussed the particular metabolic mechanisms, that L-carnitine undoubtedly represents an interesting therapeutic drug for patients with exercise-induced stable angina.

Cherchi A, Lai C, Onnis E, Orani E, Pirisi R, Pisano MR, Soro A, Corsi M.
Propionyl carnitine in stable effort angina.
Cardiovasc Drugs Ther 1990 Apr;4(2):481-6
The aim of this study was to investigate the anti-ischemic activity of propionyl carnitine (PC) in 18 informed, volunteer male patients, aged 37-70, suffering from a typical stable effort angina. The study design was randomized, balanced, crossover, and double blinded. The study lasted 75 days. In the first 15 days of washout the patients performed two maximal symptom-limited bicycle tests to verify the repeatability of the parameters examined. Then one group received PC for 30 days 500 mg three times a day, and the other group received placebo (PL) three times a day. At the end of 30 days the groups exchanged treatments. At the end of each period, 2 hours after the last oral administration, the patients performed a maximal symptom-limited bicycle exercise test with increased loads of 10 watts/min. No significant differences were observed between the two tests performed during the wash-out period, for a 1 mm ST-segment depression time, for the time to the end of exercise, and for the rate x pressure product at the same experimental time. The oral administration of PC in coronary patients increased both the 1 mm ST-segment depression time and the time to the end of exercise. Furthermore, the drug reduced the ischemic depression of ST at maximal common work and at maximal work. After PC, the rate x pressure product was not significantly different in relation to placebo at submaximal and maximal exercise. Thus PC seems to have an antiischemiclike effect, probably related to its metabolic activity.

Chronic fatigue syndrome (Chronisches Müdigkeits-Syndrom)

Plioplys AV, Plioplys S.
Amantadine and L-carnitine treatment of Chronic Fatigue Syndrome.
Neuropsychobiology 1997;35(1):16-23
Carnitine is essential for mitochondrial energy production. Disturbance in mitochondrial function may contribute to or cause the fatigue seen in Chronic Fatigue Syndrome (CFS) patients. Previous investigations have reported decreased carnitine levels in CFS. Orally administered L-carnitine is an effective medicine in treating the fatigue seen in a number of chronic neurologic diseases. Amantadine is one of the most effective medicines for treating the fatigue seen in multiple sclerosis patients. Isolated reports suggest that it may also be effective in treating CFS patients. Formal investigations of the use of L-carnitine and amantadine for treating CFS have not been previously reported. We treated 30 CFS patients in a crossover design comparing L-carnitine and amantadine. Each medicine was given for 2 months, with a 2-week washout period between medicines. L-Carnitine or amantadine was alternately assigned as fist medicine. Amantadine was poorly tolerated by the CFS patients. Only 15 were able to complete 8 weeks of treatment, the others had to stop taking the medicine due to side effects. In those individuals who completed 8 weeks of treatment, there was no statistically significant difference in any of the clinical parameters that were followed. However, with L-carnitine we found statistically significant clinical improvement in 12 of the 18 studied parameters after 8 weeks of treatment. None of the clinical parameters showed any deterioration. The greatest improvement took place between 4 and 8 weeks of L-carnitine treatment. Only 1 patient was unable to complete 8 weeks of treatment due to diarrhea. L-Carnitine is a safe and very well tolerated medicine which improves the clinical status of CFS patients. In this study we also analyzed clinical and laboratory correlates of CFS symptomatology and improvement parameters.

Claudicatio intermittens (Periphere arterielle Verschlusskrankheit)

Brevetti G, di Lisa F, Perna S, MenabÃ³ R, Barbato R, Martone VD, Siliprandi N.
Carnitine-related alterations in patients with intermittent claudication: indication for a focused carnitine therapy.
Circulation 1996 May;93(9):1685-9
BACKGROUND: Carnitine metabolism is altered in peripheral arterial disease. L-carnitine supplementation may correct these alterations and improve walking performance. METHODS AND RESULTS: Plasma levels of carnitine and its esters were measured at rest and after maximally tolerated exercise in 22 claudicant patients and 8 normal subjects. One week later, this protocol was repeated in patients after random administration of placebo or L-carnitine (500 mg IV as a single bolus). Two groups of patients emerged. In 10 patients (group IC1), the plasma level of acetylcarnitine at rest was 3.7 +/- 0.2 micromol/L and increased significantly (P<.01) at maximally tolerated exercise. In 12 patients (group IC2), the resting level of plasma acetylcarnitine was elevated (7.9 +/- 0.7 micromol/L, P<.01) and decreased with exercise. Furthermore, group IC2 patients had a significantly lower walking capacity than group IC1 patients. In both groups, placebo did not affect the metabolic profile, nor did it improve exercise performance. Conversely, after L-carnitine administration, all but one patient in group IC2 (n=7) showed an increase in plasma acetylcarnitine concentration during exercise versus the decrease observed without L-carnitine. This metabolic effect was accompanied by a significant increase (P<.01) in walking capacity. Interestingly, in group IC1 patients (n=5), L-carnitine neither improved walking capacity nor modified the metabolic profile. Statistical analysis showed that changes in walking capacity with L-carnitine treatment were influenced exclusively by exercise-induced changes in plasma acetylcarnitine. CONCLUSIONS: In patients with intermittent claudication, assessment of plasma acetylcarnitine at rest and after exercise may be a means to select a target population for L-carnitine therapy.

Brevetti G, Diehm C, Lambert D.
European multicenter study on propionyl-L-carnitine in intermittent claudication.
J Am Coll Cardiol 1999 Nov;34(5):1618-24
OBJECTIVES: This study was performed to identify a target population of claudicants for propionyl-L-carnitine treatment. BACKGROUND: Previous studies suggest that the efficacy of propionyl-L-carnitine in intermittent claudication is greater in patients with severe functional impairment than in those with mild walking disability. METHODS: After run-in, 485 claudicant patients were randomized to placebo or propionyl-L-carnitine (1 g bid, p.o.) and then stratified on the basis of maximal walking distance (cutoff point 250 m) and maximal walking distance variability (cutoff point 25%). Treatment lasted 12 months. Walking capacity was assessed by treadmill and quality of life by a questionnaire exploring various aspects of daily life. RESULTS: In the target population, that is, patients who at baseline walked < or = 250 m and showed a maximal walking distance variability < or = 25%, per-protocol analysis showed that the effect of propinyl-L-carnitine was significantly greater than that with placebo for both maximal walking distance and initial claudication distance (ICD). In the intention-to-treat population, maximal walking distance increased by 62 +/- 14% on propionyl-L-carnitine and by 46 +/- 9% (p < 0.05) on placebo, while no difference between treatments was observed for ICD. The beneficial effect of propionyl-L-carnitine was confirmed when data of the target population were pooled with those of patients who at baseline walked < or = 250 m and showed a > 25% maximal walking distance < 50% variability. Actually, maximal walking distance increased by 98 +/- 16% in the propionyl-L-carnitine group and by only 54 +/- 10% in the placebo group (p < 0.01). The corresponding values for ICD were 99 +/- 21% and 51 +/- 8% (p < 0.05). For patients with baseline maximal walking distance > 250 m, no difference between treatments was observed. CONCLUSIONS: Claudicants with maximal walking distance < or = 250 m benefited from the use of propionyl-L-carnitine, with improvement in walking distance and quality of life. However, patients with mild functional impairment (i.e., walking distance > 250 m) showed no response to propionyl-L-carnitine.
Brevetti G, Chiariello M, Ferulano G, Policicchio A, Nevola E, Rossini A, Attisano T, Ambrosio G, Siliprandi N, Angelini C.
Increases in walking distance in patients with peripheral vascular disease treated with L-carnitine: a double-blind, cross-over study.

Circulation 1988 Apr;77(4):767-73
A double-blind, cross-over study was designed to evaluate the effects of L-carnitine in patients with peripheral vascular disease. After drug washout, 20 patients were randomly assigned to receive placebo or L-carnitine (2 g bid, orally) for a period of 3 weeks and were then crossed over to the other

treatment for an additional 3 weeks. The effect on walking distance at the end of each treatment period was measured by treadmill test. Absolute walking distance rose from 174 +/- 63 m with placebo to 306 +/- 122 m (p less than .01) with carnitine. Biopsy of the ischemic muscle, carried out before and after 15 days of L-carnitine administration in four additional patients, showed that treatment significantly increased total carnitine levels. An additional goal of this study was to ascertain the effects of L-carnitine on the metabolic changes induced by exercise in the affected limb. In six patients under control conditions, arterial and popliteal venous lactate and pyruvate concentrations were determined at rest, when the maximal walking distance was reached, and 5 min after the walking test. Twenty-four hours later, L-carnitine was administered intravenously (3 g as a bolus followed by an infusion of 2 mg/kg/min for 30 min) and metabolic assessments were repeated. Five minutes after the walking test, popliteal venous lactate concentration increased by 107 +/- 16% before treatment and by only 54 +/- 32% (p less than .01) after carnitine. Furthermore, carnitine induced a more rapid recovery to the resting value of the lactate/pyruvate ratio.(ABSTRACT TRUNCATED AT 250 WORDS)

Diabetes mellitus, Typ II

Mingrone G, Greco AV, Capristo E, Benedetti G, Giancaterini A, De Gaetano A, Gasbarrini G.
L-carnitine improves glucose disposal in type 2 diabetic patients.
J Am Coll Nutr 1999 Feb;18(1):77-82

OBJECTIVE: Aim of the present study is to evaluate the effects of L-carnitine on insulin-mediated glucose uptake and oxidation in type II diabetic patients and compare the results with those in healthy controls. DESIGN: Fifteen type II diabetic patients and 20 healthy volunteers underwent a short-term (2 hours) euglycemic hyperinsulinemic clamp with simultaneous constant infusion of L-carnitine (0.28 micromole/kg bw/minute) or saline solution. Respiratory gas exchange was measured by an open-circuit ventilated hood system. Plasma glucose, insulin, non-esterified fatty acids (NEFA) and lactate levels were analyzed. Nitrogen urinary excretion was calculated to evaluate protein oxidation. RESULTS: Whole body glucose uptake was significantly ($p<0.001$) higher with L-carnitine than with saline solution in the two groups investigated (48.66+/-4.73 without carnitine and 52.75+/-5.19 micromoles/kg(ffm)/minute with carnitine in healthy controls, and 35.90+/-5.00 vs. 38.90+/-5.16 micromoles/kg(ffm)/minute in diabetic patients). Glucose oxidation significantly increased only in the diabetic group (17.61+/-3.33 vs. 16.45+/-2.95 micromoles/kg(ffm)/minute, $p<0.001$). On the contrary, glucose storage increased in both groups (controls: 26.36+/-3.25 vs. 22.79+/-3.46 micromoles/kg(ffm)/minute, $p<0.001$; diabetics: 21.28+/-3.18 vs. 19.66+/-3.04 micromoles/kg(ffm)/minute, $p<0.001$). In type II diabetic patients, plasma lactate significantly decreased during L-carnitine infusion compared to saline, going from the basal period to the end-clamp period (0.028+/-0.0191 without carnitine and 0.0759+/-0.0329 with carnitine, $p<0.0003$). CONCLUSIONS: L-carnitine constant infusion improves insulin sensitivity in insulin resistant diabetic patients; a significant effect on whole body insulin-mediated glucose uptake is also observed in normal subjects. In diabetics, glucose, taken up by the tissues, appears to be promptly utilized as fuel since glucose oxidation is increased during L-carnitine administration. The significantly reduced plasma levels of lactate suggest that this effect might be exerted through the activation of pyruvate dehydrogenase, whose activity is depressed in the insulin resistant status.

Diabetische Neuropathie
bei Personen mit *Diabetes mellitus, Typ II*

De Grandis D, Minardi C.
Acetyl-L-carnitine (levacecarnine) in the treatment of diabetic neuropathy. A long-term, randomised, double-blind, placebo-controlled study.
Drugs R D 2002;3(4):223-31
OBJECTIVE: To assess the efficacy and tolerability of acetyl-L-carnitine (levacecarnine; LAC) versus placebo in the treatment of diabetic neuropathy, mainly by evaluating the effects of treatment on electrophysiological parameters and pain symptoms. DESIGN: This was a multicentre (n = 20), randomised, double-blind, placebo-controlled, parallel-group study. PATIENTS: 333 patients meeting clinical and/or neurophysiological criteria for diabetic neuropathy were enrolled. INTERVENTIONS: Patients were randomised to treatment with LAC or placebo. LAC (or placebo) was started intramuscularly at a dosage of 1000 mg/day for 10 days and continued orally at a dosage of 2000 mg/day for the remainder of the study (355 days). MAIN OUTCOME PARAMETERS AND RESULTS: The main efficacy parameter was the effect of treatment on 6- and 12-month changes from baseline in nerve conduction velocity (NCV) and amplitude in the sensory (ulnar, sural and median) and motor (median, ulnar and peroneal) nerves. The effect of treatment on pain was also evaluated by means of a visual analogue scale (VAS). Among the 294 patients with impaired electrophysiological parameters at baseline, those treated with LAC showed a statistically significant improvement in mean NCV and amplitude compared with placebo ($p < 0.01$). The greatest changes in NCV (at 12 months) were observed in the sensory sural nerve (7 m/sec in the LAC group vs +1.0 m/sec in the placebo group), sensory ulnar nerve (+2.9 vs +0.1 m/sec, respectively) and motor peroneal nerve (+2.7 vs -0.2 m/sec), whereas the greatest changes in amplitude were recorded in the motor peroneal nerve (+2.2 vs +0.1 mV). After 12 months of treatment, mean VAS scores for pain were significantly reduced from baseline by 39% in LAC-treated patients ($p < 0.0$ vs baseline) compared with 8% in placebo recipients. LAC was well tolerated over the study period. CONCLUSIONS: LAC was effective and well tolerated in improving neurophysiological parameters and in reducing pain over a 1-year period. LAC is, therefore, a promising treatment option in patients with diabetic neuropathy.

Herzinsuffizienz

Ghidini O, Azzurro M, Vita G, Sartori G.
Evaluation of the therapeutic efficacy of L-carnitine in congestive heart failure.
Int J Clin Pharmacol Ther Toxicol 1988 Apr;26(4):217-20
To evaluate the therapeutic efficacy of L-carnitine in elderly subjects suffering from heart failure, secondary to ischemic and/or hypertensive heart disease, 38 patients (22 men, 16 women) were studied, aged from 65 to 82 years. In addition to traditional therapy (digitalis, diuretics, antiarrhythmic agents) given in all cases, 21 patients received oral L-carnitine on the basis of a randomized protocol in 1-g doses twice daily for 45 days (the other 17 received placebo). In the group treated with L-carnitine, a distinct improvement was observed in both subjective and objective conditions; reduced heart rate, edema and dyspnea, increased diuresis and a marked reduction in daily digitalis consumption. L-carnitine treatment also induced a significant reduction in serum cholesterol and triglyceride levels. No adverse reactions attributable to L-carnitine administration were observed in any of the patients.

Anand I, Chandrashekhan Y, De Giuli F, Pasini E, Mazzoletti A, Confortini R, Ferrari R.
Acute and chronic effects of propionyl-L-carnitine on the hemodynamics, exercise capacity, and hormones in patients with congestive heart failure.
Cardiovasc Drugs Ther 1998 Jul;12(3):291-9
Carnitine is an important cofactor in the intermediary metabolism of the heart, and carnitine deficiency is associated with congestive heart failure. We therefore studied the effects of acute (IV bolus, 30 mg/kg body weight) and chronic administration (1.5 mg/d for 1 month) of propionyl-L-carnitine on hemodynamics, hormone levels, ventricular function, exercise capacity, and peak oxygen consumption in 30 patients with chronic congestive heart failure (NYHA II-III, mean EF 29.5 +/- 7%) in a phase II, parallel, single-blind, randomized, and placebo-controlled study. Acute administration of propionyl-L-carnitine caused a significant reduction in pulmonary artery and pulmonary wedge pressures at both day 1 ($P < 0.001$) and day 30 ($P < 0.05$) of the study but no other hemodynamics changes. Hormone levels did not change following acute administration of the drug. Chronic administration of propionyl-L-carnitine increased peak oxygen consumption by 45% (from 16.0 +/- 3 to 23.5 +/- 2 mL/kg/min, P +/- 0.001), exercise time by 21% (from 8.1 +/- 0.5 to 9.8 +/- 0.4 minutes, $P < 0.01$), and peak exercise heart rate by 12% ($P < 0.01$). These changes were concomitant with a reduction of pulmonary artery pressure. In the treated group, there was a slight, but significant ($P < 0.01$), reduction in left ventricular dimensions. Hemodynamics and hormones measured after 1 month of oral therapy remained unchanged, except for a fall in pulmonary artery pressures, with a nonsignificant trend towards a fall in filling pressures and plasma norepinephrine. The chronic changes in the propionyl-L-carnitine group were seen at 15 days of treatment, and no further changes in these parameters were seen at 1 month. We conclude that propionyl-L-carnitine increases exercise capacity and reduces ventricular size in patients with congestive heart failure. The drug has no significant effects on hemodynamics or neurohormone levels. The use of a single-blind design reduces the impact of the positive finding on exercise capacity.

Mancini M, Rengo F, Lingetti M, Sorrentino GP, Nolfe G.
Controlled study on the therapeutic efficacy of propionyl-L-carnitine in patients with congestive heart failure.
Arzneimittelforschung 1992 Sep;42(9):1101-4
A double-blind phase II study of propionyl-L-carnitine (CAS 17298-37-2) versus placebo was carried out on a group of 60 patients with mild to moderate (II and III NYHA class) congestive heart failure. The group was made up of men and women aged between 48 and 73 years in chronic treatment with digitalis and diuretics for at least 3 months and who still displayed symptoms. Thirty of these patients were chosen randomly and for 180 days, 500 mg of propionyl-L-carnitine was orally administered, 3 times a day in addition to their usual treatment. At basal conditions and after 30, 90 and 180 days the maximum exercise time was evaluated using an exercise tolerance test performed on an ergometer bicycle and the left ventricular ejection fraction was tested by means of bidimensional echocardiography. After one month of treatment, the patients treated with propionyl-L-carnitine, compared to the control group, showed significant increases in the values of both tests, increases which became even more evident after 90 and 180 days. At the stated times the increases in the maximum exercise time were 16.4%, 22.9%, and 25.9%, respectively. The ventricular ejection fraction increased by 8.4%, 11.6% and 13.6%, respectively. On the basis of these results, having studied the particular mechanism of action of propionyl-L-carnitine the authors conclude that it represents a drug

of undoubted therapeutic interest in patients with congestive heart failure, in whom it could be efficaciously administered along with a standard pharmacological therapy.

Caponnetto S, Canale C, Masperone MA, Terracchini V, Valentini G, Brunelli C.
Efficacy of L-propionylcarnitine treatment in patients with left ventricular dysfunction.
Eur Heart J 1994 Sep;15(9):1267-73
The effect of L-propionylcarnitine on patients with left ventricular dysfunction (EF < 45%) NYHA class II, symptomatic despite therapy with digitalis and diuretics was evaluated in a phase II parallel, double-blind, randomized, placebo-controlled study. Fifty patients (28 men and 22 women) aged 37-70 years received 1.5 g of L-propionylcarnitine or placebo on a random basis as oral treatment for 6 months. At baseline, during a 7 day placebo run-in period, and during the 6-month treatment bicycle exercise test, M-B mode and Doppler echocardiography, and clinical evaluation (clinical score) were repeatedly performed. The analysis of variance for repeated measurements showed a statistically significant difference ($P < 0.01$) in the mean value of exercise time between the treatments over the period of the study. There was a final increase of 0.36 min in the placebo group, 1.4 min in the treated group and a minor production of lactate during exercise in the treated group. Left ventricular shortening fraction and left ventricular ejection fraction showed a significant increase in the L-propionylcarnitine group (respectively $P < 0.01$ and $P < 0.0001$) whereas no difference was apparent in the placebo group. Stroke volume index and cardiac index showed significant increments in the treated group ($P < 0.05$) and systemic vascular resistance was lowered ($P < 0.05$). No haemodynamic variations were observed in the placebo group, and the clinical score showed a significant improvement in the L-propionylcarnitine treated group. In conclusion, L-propionylcarnitine treatment was shown to improve patient symptomatology and effort tolerance.

HIV

Moretti S, Alesse E, Di Marzio L, Zazzeroni F, Ruggeri B, Marcellini S, Famularo G, Steinberg SM, Boschini A, Cifone MG, De Simone C.
Effect of L-carnitine on human immunodeficiency virus-1 infection-associated apoptosis: a pilot study.
Blood 1998 May;91(10):3817-24
The Fas/Fas ligand system is involved in uncontrolled apoptosis, which ultimately leads to the loss of T lymphocytes in human immunodeficiency virus (HIV)-infected individuals. The signal transduced by Fas receptor involves the activation of an acidic sphingomyelinase, sphingomyelin breakdown, and ceramide production. Our recent reports have shown that L-carnitine inhibits Fas-induced apoptosis and ceramide production both in vitro and in vivo. The aim of this study was to study, in a preliminary fashion, the impact of long-term L-carnitine administration on CD4 and CD8 absolute counts, rate, and apoptosis in HIV-1-infected subjects. The generation of cell-associated ceramide and HIV-1 viremia was also investigated. Eleven, asymptomatic, HIV-1-infected subjects, who refused any antiretroviral treatment despite experiencing a progressive decline of CD4 counts, were treated with daily infusions of L-carnitine (6 g) for 4 months. Immunologic and virologic measures and safety were monitored at the start of the treatment and then on days 15, 30, 90, and 150. L-carnitine therapy resulted in an increase of absolute CD4 counts, which was statistically significant on day 90 and 150 (P = . 010 and P = .019, respectively). A positive, not significant trend was also observed even in the change in absolute counts of CD8 lymphocytes. L-carnitine therapy also led to a drop in the frequency of apoptotic CD4 and CD8 lymphocytes. This reduction occurred gradually, but changes in actual values between each time point and baseline were strongly significant (P = .001 at the end of the study compared with the baseline). A strong reduction (P = .001) in cell-associated ceramide levels was found at the end of the study. In general, HIV-1 viremia increased slightly. No toxicity related to L-carnitine therapy was observed and dose reductions were not necessary. In HIV-1-infected subjects, long-term infusions of L-carnitine produced substantial increases in the rate and absolute counts of CD4 and, to a lesser degree, of CD8 lymphocytes. This was paralleled by a reduced frequency of apoptotic cells of both subgroups and a decline in the levels of ceramide. No clinically relevant change of HIV-1 viremia was observed.

Moretti S, Famularo G, Marcellini S, Boschini A, Santini G, Trinchieri V, Lucci L, Alesse E, De Simone C.
L-carnitine reduces lymphocyte apoptosis and oxidant stress in HIV-1-infected subjects treated with zidovudine and didanosine.
Antioxid Redox Signal 2002 Jun;4(3):391-403
Apoptosis is critical to the progression of human immunodeficiency virus-1 (HIV-1) infection. It appears reasonable that antiretroviral therapies may not achieve a full control of the infection in the absence of an impact on apoptosis. We assigned 20 asymptomatic HIV-infected subjects with advanced immunodeficiency to receive either zidovudine (AZT), and didanosine (DDI) or the same regimen plus L-carnitine, a known antiapoptotic drug, for 7 months. Immunologic and virologic parameters were measured at baseline and after 15, 60, 120, and 210 days of treatment. We assessed on each time point the following: (a) the frequency of peripheral blood apoptotic CD4 and CD8 lymphocytes, CD4 and CD8 cells with disrupted mitochondrial membrane potential, and CD4 and CD8 cells undergoing oxidant stress; (b) the expression of the molecular markers of apoptosis Fas and caspase-1; and (c) the expression of p35/cdk-5 regulatory subunit that is involved in regulating cell survival and apoptosis. Absolute CD4 and CD8 counts and plasma viremia were also measured. Apoptotic CD4 and CD8 cells, lymphocytes with disrupted mitochondrial membrane potential, and lymphocytes undergoing oxidant stress were greatly reduced in subjects treated with AZT and DDI plus L-carnitine compared with those who did not receive L-carnitine. Fas and caspase-1 were down-expressed and p35 over-expressed in lymphocytes from patients of the L-carnitine group. No difference was found in CD4 and CD8 counts and viremia between the groups. No toxicity of L-carnitine was recognized. The addition of L-carnitine is safe and allows apoptosis and oxidant stress to be greatly reduced in lymphocytes from subjects treated with AZT and DDI.

De Simone C, Tzantzoglou S, Famularo G, Moretti S, Paoletti F, Vullo V, Delia S.
High dose L-carnitine improves immunologic and metabolic parameters in AIDS patients.
Immunopharmacol Immunotoxicol 1993 Jan;15(1):1-12
Several reports indicate that systemic carnitine deficiency could occur in acquired immunodeficiency disease syndrome (AIDS), and that primary and secondary carnitine deficiency leads to critical metabolic dysfunctions. L-carnitine supplementation to peripheral blood mononuclear cells (PBMCs) of AIDS patients resulted in significant enhancement of the phytohemagglutinin (PHA)-driven proliferative

response. High dose L-carnitine administration (6 gr per day for two weeks) to AIDS patients treated with zidovudine also led to increased PBMCs proliferation and reduced blood levels of triglycerides. In addition, a reduction of beta 2-microglobulin serum levels as well as circulating tumor necrosis factor (TNF)-alpha, mostly in patients exhibiting highly elevated levels, were found at the end of the treatment period. Our data suggest that in vivo L-carnitine could prove useful in ameliorating both the immune response and lipid metabolism in patients with AIDS, irrespective of initial serum carnitines levels. The mechanism(s) accounting for the observed results are currently not clear. Further studies are needed to confirm the hypothesis that L-carnitine affects the expression of HIV-induced cytokine.

Hyperlipoproteinämie
bei Personen mit *Diabetes mellitus, Typ II*

Derosa G, Cicero AF, Gaddi A, Mugellini A, Ciccarelli L, Fogari R.
The effect of L-carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus.
Clin Ther 2003 May;25(5):1429-39
BACKGROUND: A previous study has demonstrated that L-carnitine reduces plasma lipoprotein(a) (Lp[a]) levels in patients with hypercholesterolemia. OBJECTIVE: To test a tolerable Lp(a)-reducing agent in diabetic patients, we assessed the effect of a dietary supplementation of L-carnitine on plasma lipid levels, particularly Lp(a), of patients with type 2 diabetes mellitus (DM) and hypercholesterolemia. METHODS: In this 6-month, randomized, double-masked, placebo-controlled clinical trial, patients were enrolled, assessed, and followed up at the Diabetic and Metabolic Diseases Center of the Department of Internal Medicine and Therapeutics at the University of Pavia, Pavia, Italy. All study patients had newly diagnosed type 2 DM that was managed through dietary restriction alone throughout the study, as well as hypercholesterolemia. Patients were randomized to 1 of 2 groups. One group received L-carnitine, one 1-g tablet BID. The other group received a corresponding placebo. We assessed body mass index, fasting plasma glucose, postprandial plasma glucose, glycosylated hemoglobin, fasting plasma insulin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, apolipoprotein (apo) A-I, apo B, and Lp(a) at baseline and at 1, 3, and 6 months of treatment. RESULTS: This study included 94 patients. The treatment group included 24 men and 22 women (mean [SD] age, 52 [6] years). The placebo group included 23 men and 25 women (mean [SD] age, 50 [7] years). The baseline characteristics of the groups did not differ significantly. The mean (SD) body weight, height, and body mass index were 78.2 (5.8) kg, 1.70 (0.04) m, and 27.3 (2.5) kg/m(2), respectively, in the L-carnitine group and 77.6 (6.4) kg, 1.71 (0.05) m, and 26.8 (2.2) kg/m(2), respectively, in the placebo group. In the treatment group, Lp(a) was significantly reduced at 3 and 6 months compared with baseline ($P < 0.05$) and $P < 0.01$, respectively). We observed a significant improvement after 6 months ($P < 0.05$) in the Lp(a) value in patients taking L-carnitine compared with those taking placebo. Between-group differences in other variables did not reach a level of significance at months 3 and 6. No drug-related adverse events were reported or observed. CONCLUSION: In this preliminary study, after 3 and 6 months, L-carnitine significantly lowered the plasma Lp(a) level compared with placebo in selected hypercholesterolemic patients with newly diagnosed type 2 DM.

Hyperthyreose

Benvenga S, Ruggeri RM, Russo A, Lapa D, Campenni A, Trimarchi F.
Usefulness of L-carnitine, a naturally occurring peripheral antagonist of thyroid hormone action, in iatrogenic hyperthyroidism: a randomized, double-blind, placebo-controlled clinical trial.
J Clin Endocrinol Metab 2001 Aug;86(8):3579-94
Old studies in animals and unblinded studies in a few hyperthyroid patients suggested that L -carnitine is a periferal antagonist of thyroid hormone action at least in some tissues. This conclusion was substantiated by our recent observation that carnitine inhibits thyroid hormone entry into the nucleus of hepatocytes, neurons, and fibroblasts. In the randomized, double-blind, placebo-controlled 6-month trial reported here, we assessed whether 2 or 4 g/d oral L-carnitine were able to both reverse and prevent/minimize nine hyperthyroidism- related symptoms. We also evaluated changes on nine thyroid hormone-sensitive biochemical parameters and on vertebral and hip mineral density (bone mineral density). Fifty women under a fixed TSH-suppressive dose of L -T(4) for all 6 months were randomly allocated to five groups of 10 subjects each. Group 0 associated placebo for 6 months; groups A2 and A4 started associating placebo (first bimester), substituted placebo with 2 or 4 g/d carnitine (second bimester), and then returned to the association with placebo. Groups B2 and B4 started associating 2 and 4 g/d carnitine for the first two bimesters, and then substituted carnitine with placebo (third bimester). Symptoms and biochemical parameters worsened in group 0. In group A, symptoms and biochemical parameters worsened during the first bimester, returned to baseline or increased minimally during the second bimester (except osteocalcin and urinary OH-proline), and worsened again in the third bimester. In group B, symptoms and biochemical parameters (except osteocalcin and urinary OH-proline) did not worsen or even improved over the first 4 months; they tended to worsen in the third bimester. In both the A and B groups, the two doses of carnitine were similarly effective. At the end of the trial, bone mineral density tended to increase in groups B and A (B > A). In conclusion, L-carnitine is effective in both reversing and preventing symptoms of hyperthyroidism and has a beneficial effect on bone mineralization. Because hyperthyroidism depletes the body deposits of carnitine and since carnitine has no toxicity, teratogenicity, contraindications and interactions with drugs, carnitine can be of clinical use.

Koronare Herzkrankheit

Singh RB, Aslam M.
L-carnitine administration in coronary artery disease and cardiomyopathy.
J Assoc Physicians India 1998 Sep;46(9):801-5
Myocardial ischaemia may be defined as a deficiency in cardiac energy supply relative to energy demand. In coronary artery disease (CAD), oxygen supply is limited due to coronary obstruction so energy production is not enough to meet the energy demands for work. Several reports involving about 2500 patients of CAD where carnitine was administered for upto 1 year indicate some beneficial effects. There is reduction in ischaemia showing reduced ST-segment depression and angina, greater effort tolerance and decreased need of cardiac drugs. Carnitine can cause overall improvement in cardiac performance in patients with CAD as well as in cardiomyopathy. More studies are necessary to demonstrate where carnitine can scavenge free radicals apart from its beneficial effect on fatty acid metabolism. Side effects of carnitine are mild nausea and vomiting and dose upto 2 g/day in 3 divided doses may not have any side effects. Intravenous L-carnitine acts rapidly and has no side effects.

Leistungsfähigkeit
– bei Personen im *Leistungssport*

Marconi C, Sassi G, Carpinelli A, Cerretelli P.
Effects of L-carnitine loading on the aerobic and anaerobic performance of endurance athletes.
Eur J Appl Physiol Occup Physiol 1985;54(2):131-5
L-Carnitine (L-C), a well known physiological carrier across the inner mitochondrial membrane of activated long chain fatty acids and acceptor of acyl groups from acyl-CoA, has been recently synthesised industrially. This has made it possible to study the effects of L-C loading (4 g X d(-1) by mouth over a period of 2 weeks) on the aerobic and anaerobic performance of 6 long distance competitive walkers. As a result of the treatment: 1) mean total, free and esterified serum L-C both at rest and shortly after completing a 120 min walk at about 65% of the individual maximal aerobic power (VO2max) were significantly increased; 2) VO2max increased 6%, from 54.5 +/- 3.7 (S.D.) to 57.8 +/- 4.7 m1O2 X kg(-1) X min(-1) (P less than 0.02); 3) blood lactate concentration (Lab) as a consequence of short bouts repeated exercise (series of 10, 15 and 20 jumps off both feet on a force platform) was unchanged; 4) heart rate, pulmonary ventilation, oxygen consumption, and respiratory quotient in the same conditions as for 1) were unchanged. It is concluded that, in trained athletes, as a consequence of L-C loading VO2max is slightly but significantly raised, probably as a result of an activation of substrate flow through the TCA cycle, whereas the lipid contribution to metabolism in prolonged submaximal exercise remains unchanged.

Männliche Unfruchtbarkeit

Vicari E, Calogero AE.
Effects of treatment with carnitines in infertile patients with prostato-vesiculo-epididymitis.
Hum Reprod 2001 Nov;16(11):2338-42
BACKGROUND: We have recently shown that patients with prostato-vesiculo-epididymitis (PVE) have a greater reactive oxygen species (ROS) overproduction than patients with prostatitis or prostato-vesiculitis. Since this biochemical stress persists even after treatment with antimicrobials, it may relate to an imbalance between pro- and anti-oxidant factors at the epididymal level. METHODS: To evaluate the effects of antioxidant treatment of patients with PVE, whether in the presence or absence of pro-oxidant factors, abacterial PVE infertile patients with normal (<1x10(6)/ml, group A, n = 34) or abnormal (>1x10(6)/ml, group B, n = 20) seminal white blood cell (WBC) concentrations received carnitines (L-carnitine 1 g and acetyl-carnitine 0.5 g twice/day) for 3 months followed by a wash-out period of 3 months. Semen parameters, ROS production and pregnancy outcome were evaluated before, during and following carnitine treatment. RESULTS: Carnitines increased sperm forward motility and viability in group A patients. This was associated with a significant reduction in ROS production which persisted during wash-out. Carnitines increased only the percentage of viable spermatozoa in group B patients. Within 3 months after the discontinuation of carnitines, the rate of spontaneous pregnancy in group A patients was significantly higher than that of group B patients, being 11.7% (4/34) compared with 0%. CONCLUSION: These results indicate that carnitines are only an effective treatment in patients with abacterial PVE and elevated ROS production when seminal WBC concentration is normal.

Vitali G, Parente R, Melotti C.
Carnitine supplementation in human idiopathic asthenospermia: clinical results.
Drugs Exp Clin Res 1995;21(4):157-9
On the basis of reported experimental and clinical studies we investigated the effectiveness of L-carnitine administration in a group of patients with idiopathic asthenospermia. A favourable effect of the compound on sperm motility and rapid linear progression has been shown in 37 out of 47 patients treated. In addition, the total number of sperms increased. L-carnitine was supplemented orally by a daily dosage of 3 g for three months.

Lenzi A, Lombardo F, SgrÃ² P, Salacone P, Caponecchia L, Dondero F, Gandini L.
Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial.
Fertil Steril 2003 Feb;79(2):292-300
OBJECTIVE: To determine the efficacy of L-carnitine therapy in selected cases of male factor infertility. DESIGN: Placebo-controlled, double-blind, crossover trial. SETTING: University tertiary referral center. PATIENT(S): One hundred infertile patients (ages 20-40 years) with the following baseline sperm selection criteria: concentration, 10-20 x 10(6)/mL; total motility, 10%-30%; forward motility, <15%; atypical forms, <70%; velocity, 10-30 micro/s; linearity, <4. Eighty-six patients completed the study. INTERVENTION(S): Patients underwent L-carnitine therapy 2 g/day or placebo; the study design was 2 months of washout, 2 months of therapy/placebo, 2 months of washout, and 2 months placebo/therapy. MAIN OUTCOME MEASURE(S): Variation in sperm parameters used in the patients selection criteria, in particular, sperm motility.Excluding outliers, a statistically significant improvement in semen quality, greater than after the placebo cycle, was seen after the L-carnitine therapy for sperm concentration and total and forward sperm motility. The increase in forward sperm motility was more significant in those patients with lower initial values, i.e., <5 x 10(6) or <2 x 10(6) of forward motile sperm/ejaculate or sperm/mL. CONCLUSION(S): Based on a controlled study of efficacy, L-carnitine therapy was effective in increasing semen quality, especially in groups with lower baseline levels. However, these results need to be confirmed by larger clinical trials and in vitro studies.

Morbus Alzheimer

Spagnoli A, Lucca U, Menasce G, Bandera L, Cizza G, Forloni G, Tettamanti M, Frattura L, Tiraboschi P, Comelli M.
Long-term acetyl-L-carnitine treatment in Alzheimer's disease.
Neurology 1991 Nov;41(11):1726-32
In a double-blind, placebo-controlled, parallel-group, randomized clinical trial, we studied the efficacy of long-term (1-year) oral treatment with acetyl-L-carnitine in 130 patients with a clinical diagnosis of Alzheimer's disease. We employed 14 outcome measures to assess functional and cognitive impairment. After 1 year, both the treated and placebo groups worsened, but the treated group showed a slower rate of deterioration in 13 of the 14 outcome measures, reaching statistical significance for the Blessed Dementia Scale, logical intelligence, ideomotor and buccofacial apraxia, and selective attention. Adjusting for initial scores with analysis of covariance, the treated group showed better scores on all outcome measures, reaching statistical significance for the Blessed Dementia Scale, logical intelligence, verbal critical abilities, long-term verbal memory, and selective attention. The analysis for patients with good treatment compliance showed a greater drug benefit than for the overall sample. Reported adverse events were relatively mild, and there was no significant difference between the treated and placebo groups either in incidence or severity.

Passeri M, Cucinotta D, Bonati PA, Iannuccelli M, Parnetti L, Senin U.
Acetyl-L-carnitine in the treatment of mildly demented elderly patients.
Int J Clin Pharmacol Res 1990;10(1-2):75-9
It has been hypothesized that acetyl-L-carnitine has a cholinomimetic action. It is for this reason that it has been used in the therapy of Alzheimer's type senile dementia impairment. In the present controlled double-blind study the authors followed two randomized homogeneous groups of both sexes of 30 patients each, aged over 65 years and suffering from mild mental impairment. One group of patients underwent therapy with acetyl-L-carnitine, 2 g/day for three months, while the other group was treated with a placebo. The statistical evaluation of the results was carried-out using non-parametric methods (Friedman-Nemenyi two-way ANOVA). It was possible to affirm that the acetyl-L-carnitine treated patients showed statistically significant improvement in the behavioural scales, in the memory tests, in the attention barrage test and in the Verbal Fluency test. These satisfactory results confirm the therapeutic importance of acetyl-L-carnitine in the treatment of elderly patients with mental impairment, which could be related principally to acetylcholine defects.

Pettegrew JW, Klunk WE, Panchalingam K, Kanfer JN, McClure RJ.
Clinical and neurochemical effects of acetyl-L-carnitine in Alzheimer's disease.
Neurobiol Aging 1995 Jan-Feb;16(1):1-4
In a double-blind, placebo study, acetyl-L-carnitine was administered to 7 probable Alzheimer's disease patients who were then compared by clinical and 31P magnetic resonance spectroscopic measures to 5 placebo-treated probable AD patients and 21 age-matched healthy controls over the course of 1 year. Compared to AD patients on placebo, acetyl-L-carnitine-treated patients showed significantly less deterioration in their Mini-Mental Status and Alzheimer's Disease Assessment Scale test scores. Furthermore, the decrease in phosphomonoester levels observed in both the acetyl-L-carnitine and placebo AD groups at entry was normalized in the acetyl-L-carnitine-treated but not in the placebo-treated patients. Similar normalization of high-energy phosphate levels was observed in the acetyl-L-carnitine-treated but not in the placebo-treated patients. This is the first direct in vivo demonstration of a beneficial effect of a drug on both clinical and CNS neurochemical parameters in AD.

Myokardinfarkt

Pauly DF, Pepine CJ.
The role of carnitine in myocardial dysfunction.
Am J Kidney Dis 2003 Apr;41(4 Suppl 4):S35-43
L-Carnitine (carnitine) may have a role in the treatment of various cardiac disorders because of its actions on cardioprotection from hypoxia and oxidative stress. Studies on the role of carnitine administration to patients with myocardial infarction (MI), angina, and congestive heart failure generally have been positive. In general, treatment with carnitine (1.5 to 6 g/d for up to 1 year) results in a beneficial effect of fewer deaths and less heart failure when administered to patients after MI. Compared with placebo, carnitine use resulted in smaller increases in left ventricular end-systolic and end-diastolic volumes over time. In shorter term studies (1 to 3 months), carnitine therapy may have positive effects on symptoms of heart failure and angina in the post-MI period. Carnitine also seems to improve exercise tolerance and oxygen consumption in moderate to severe heart failure. Only preliminary results are available; results of a long-term (3-year) study should be reported soon. Studies specific to the dialysis population have generally shown that carnitine may have a beneficial effect on a number of cardiac parameters. Because cardiac disease is the most common form of death in patients with end-stage renal disease, these findings may be particularly important for this population. Moreover, because the relationship between conventional cardiac risk factors and cardiac disease is less clear in this population, the role of therapies that address pathological states specific to the dialysis population is worthy of study. Because a dialysis-related carnitine disorder is common among these patients, L-carnitine supplementation would be among these specific therapies.

Davini P, Bigalli A, Lamanna F, Boem A.
Controlled study on L-carnitine therapeutic efficacy in post-infarction.
Drugs Exp Clin Res 1992;18(8):355-65
A controlled study was carried out on 160 patients of both sexes (age between 39 and 86 years) discharged from the Cardiology Department of the Santa Chiara Hospital, Pisa, with a diagnosis of recent myocardial infarction. L-carnitine was randomly administered to 81 patients at an oral dose of g 4/die for 12 months, in addition to the pharmacological treatment generally used. For the whole period of 12 months, these patients showed, in comparison with the controls, an improvement in heart rate ($p < 0.005$), systolic arterial pressure ($p < 0.005$) and diastolic arterial pressure (NS); a decrease of anginal attacks ($p < 0.005$), of rhythm disorders (NS) and of clinical signs of impaired myocardial contractility (NS), and a clear improvement in the lipid pattern ($p < 0.005$). The above changes were accompanied by a lower mortality in the treated group (1.2%, $p < 0.005$), while in the control group there was a mortality of 12.5%. Furthermore, in the control group there was a definite prevalence of deaths caused by reinfarction and sudden death. On the basis of these results, it is concluded that L-carnitine represents an effective treatment in post-infarction ischaemic cardiopathy, since it can improve the clinical evolution of this pathological condition as well as the patient's quality of life and life expectancy.

Iliceto S, Scrutinio D, Bruzzi P, D'Ambrosio G, Boni L, Di Biase M, Biasco G, Hugenholtz PG, Rizzon P.
Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial.
J Am Coll Cardiol 1995 Aug;26(2):380-7
OBJECTIVES. This study was performed to evaluate the effects of L-carnitine administration on long-term left ventricular dilation in patients with acute anterior myocardial infarction. BACKGROUND. Carnitine is a physiologic compound that performs an essential role in myocardial energy production at the mitochondrial level. Myocardial carnitine deprivation occurs during ischemia, acute myocardial infarction and cardiac failure. Experimental studies have suggested that exogenous carnitine administration during these events has a beneficial effect on function. METHODS. The L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial was a randomized, double-blind, placebo-controlled, multicenter trial in which 472 patients with a first acute myocardial infarction and high quality two-dimensional echocardiograms received either placebo (239 patients) or L-carnitine (233 patients) within 24 h of onset of chest pain. Placebo or L-carnitine was given at a dose of 9 g/day intravenously for the first 5 days and then 6 g/day orally for the next 12 months. Left ventricular volumes and ejection fraction were evaluated on admission, at discharge from hospital and at 3, 6 and 12 months after acute myocardial infarction. RESULTS. A significant attenuation of left ventricular dilation in the first year after acute myocardial infarction was observed in patients treated with L-carnitine compared with those receiving placebo. The percent increase in both end-diastolic and end-

systolic volumes from admission to 3-, 6- and 12-month evaluation was significantly reduced in the L-carnitine group. No significant differences were observed in left ventricular ejection fraction changes over time in the two groups. Although not designed to demonstrate differences in clinical end points, the combined incidence of death and congestive heart failure after discharge was 14 (6%) in the L-carnitine treatment group versus 23 (9.6%) in the placebo group (p = NS). Incidence of ischemic events during follow-up was similar in the two groups of patients. CONCLUSIONS. L-Carnitine treatment initiated early after acute myocardial infarction and continued for 12 months can attenuate left ventricular dilation during the first year after an acute myocardial infarction, resulting in smaller left ventricular volumes at 3, 6 and 12 months after the emergent event.