**REVIEW ARTICLE**

# CARNICARE™ ™ (L-CARNITINE - L-TARTRATE-725mg) - THE SUPER NUTRIENT

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**ABSTRACT**

L-Carnitine is a trimethylated amino acid, roughly similar in structure to choline, L-carnitine is a cofactor required for transformation of free long-chain fatty acids into acylcarnitines, and for their subsequent transport into the mitochondrial matrix, where they undergo beta-oxidation for cellular energy production. Conditions that appear to benefit from exogenous supplementation of L-Carnitine include anorexia, chronic fatigue, cardiovascular disease, diphtheria, hypoglycemia, male infertility, muscular myopathies, and Rett syndrome. Preterm infants, dialysis patients, and HIV-positive individuals seem to be prone to a deficiency of L-Carnitine and benefit from supplementation. Although discovered in 1905, the crucial role of L-carnitine in metabolism was not elucidated until 1955, and its deficiency was not described until 1972. The most significant source of L-Carnitine in human nutrition is meat, although humans can synthesize L-Carnitine from dietary amino acids. This review discusses the role of L-Carnitine in Clinical Indications Such as Anorexia, Athletic Performance. In Cardiovascular Diseases such as Angina and Ischemia, Peripheral Vascular Disease, Cardiogenic Shock, Cardiomyopathy, MyocardialInfarction, Hyperlipidemia,Diabetes/Insulin Resistance, Cancer, & in Hepatic Effects such as Fatty Liver,Hepatitis, Hepatic Encephalopathy from Cirrhosis, HIV and Immunity, Hyperthyroidism,Male Infertility, Renal Failure/Dialysis, Weight Loss,Respiratory Distress in Premature Infants.

## INTRODUCTION

### What is L-carnitine?

1. L-Carnitine is a vitamin-like nutrient related to vitamins of the B-group

2. L-Carnitine is a physiological substance, essential for energy production and for fat metabolism.

3. In international classification, L-Cartinine is listed next to choline, another vitamin-like nutrient.

4. L-Carnitine can be synthesized in the human liver and kidney, but insufficient amount may be produced in infants, in adolescents and in adults under certain physiological conditions.

## SOURCES OF L-CARNITINE

L-Carnitine is supplied to the human body via both food intake and endogenous synthesis (we can make it ourselves in our bodies). Dietary sources of L-Carnitine are confined mainly to foods of animal

origin, particularly red meat (this obviously has important implication for vegetarians) and dietary L-Carnitine is absorbed in the small intestine. Endogenous synthesis requires six other nutrients, including amino acids, vitamins and iron. Since synthesis takes place primarily in the liver and kidney, the skeletal muscle and the heart, which depend upon fat breakdown for energy, are highly dependent on L-Carnitine transport from the site of synthesis.

A trimethylated amino acid, roughly similar in structure to choline, L-carnitine is a cofactor required for transformation of free long-chain fatty acids into acylcarnitines, and for their subsequent transport into the mitochondrial matrix, where they undergo beta-oxidation for cellular energy production. Conditions that appear to benefit from exogenous supplementation of L-carnitine include anorexia, chronic fatigue, cardiovascular disease, diphtheria, hypoglycemia, male infertility, muscular myopathies, and Rett syndrome. Preterm infants, dialysis patients, and HIV-positive individuals seem to be prone to a deficiency of L-carnitine and benefit from supplementation.

Although discovered in 1905, the crucial role of L-carnitine in metabolism was not elucidated until 1955, and its deficiency was not described until 1972. The most significant source of L-carnitine in human nutrition is meat, although humans can synthesize L-carnitine from dietary amino acids.

## BIOCHEMISTRY AND PHARMACOKINETICS

Synthesis of carnitine begins with methylation of the amino acid L-lysine by S-adenosylmethionine (SAMe). Magnesium, vitamin C, iron, vitamins B3 and B6, and alpha-ketoglutarate – along with the cofactors responsible for creating SAMe (methionine, folic acid, vitamin B12, and betaine) – are all required for endogenous carnitine synthesis.

Evidence indicates L-carnitine is absorbed in the intestine by a combination of active transport and passive diffusion.1 Reports of bioavailability following an oral dose have varied substantially, with estimates as low as 16-18 percent2,3 and as high as 54-87 percent.4,5

Oral supplementation of L-carnitine in individual dosages greater than 2 g appears to offer no advantage, since the mucosal absorption of carnitine appears to be saturated at about a 2-g dose.2 Maximum blood concentration is reached approximately 3.5 hours after an oral dose and slowly decreases, with a half-life of about 15 hours.4 Elimination of carnitine occurs primarily through the kidneys.4

The heart, skeletal muscle, liver, kidneys, and epididymis have specific transport systems for carnitine that concentrate carnitine within these tissues. Despite evidence indicating increased levels of free carnitine and carnitine metabolites in the blood and urine following an oral dose, no significant change in red blood cell carnitine levels was noted in healthy subjects, suggesting either a slow repletion of tissue stores of carnitine following an oral dose or a low capability to transport carnitine into tissues under normal conditions.6

## MECHANISMS OF ACTION

Carnitine□s primary mechanism of action is apparently attributable to its role as a cofactor in the transformation of free long-chain fatty acids into acylcarnitines for subsequent transport into the mitochondrial matrix.7

Carnitine is involved in the metabolism of ketones for energy8 and the conversion of branched-chain amino acids – valine, leucine, and isoleucine – into energy.9

## DEFICIENCY STATES AND SYMPTOMS

Although L-carnitine is supplied exogenously as a component of the diet and can also be synthesized endogenously, evidence suggests both primary and secondary deficiencies do occur. Carnitine deficiency can be acquired or a result of inborn errors of metabolism.10

Pre-term infants are at risk for developing a carnitine deficiency due to impaired synthesis and insufficient renal tubular resorption.11

Primary carnitine deficiency, although rare, is characterized by low plasma, red blood cell, and tissue levels of carnitine, and generally presents with symptoms such as muscle fatigue, cramps, and myoglobinemia following exercise. Additional symptoms of chronic carnitine deficiency can include hypoglycemia, progressive myasthenia, hypotonia, or lethargy.

Secondary carnitine deficiency is not as rare and is most commonly associated with dialysis in chronic renal failure, although it can also be induced by intestinal resection, severe infection, and liver disease. Other conditions associated with a carnitine deficiency include cancer,12 diabetes, Alzheimer□s disease, and heart failure.11

Pathological manifestations of chronic deficiency include accumulation of neutral lipid within skeletal muscle, cardiac muscle, and liver; a disruption of muscle fibers; and an accumulation of large aggregates of mitochondria within skeletal and smoothmuscle

## CLINICAL INDICATIONS

### *Anorexia*

Combined use of L-carnitine and adenosylcobalamin in patients with anorexia nervosa has been shown to accelerate body weight gain, normalize gastrointestinal function, decrease fatigue, and improve physical performance.13,14 Children with infantile anorexia responded to a combination of carnitine and adenosylcobalamin with improved appetite.15

### *Athletic Performance*

A clinical study reported improved running speed and decreased average oxygen consumption and heart rate following prolonged L-carnitine supplementation,16 while other researchers reported increased maximal oxygen uptake and decreased plasma lactate when L-carnitine was supplemented acutely one hour prior to beginning exercise.17 A small study on L-carnitine□s effect on high-repetition squat exercise found significant benefit from 2 g carnitine daily compared to placebo on blood parameters of muscle recovery – myoglobin, creatine kinase, and malondialdehyde.18 In contrast, other research has shown no ergogenic effects of either chronic or acute L-carnitine supplementation.19-21

### *Cardiovascular Disease*

#### Angina and Ischemia

L-carnitine (oral doses ranging from 900-3,000 mg daily) has been shown to moderately improve exercise tolerance and reduce ECG indices of ischemia in patients with stable angina. Estimates suggest upward of 22 percent of subjects might become angina-free during supplementation periods. Increasing benefits are often observed with longer supplementation.22-25

Angina patients receiving L-carnitine have experienced functional improvement, including a reduction in the number of premature ventricular contractions at rest, an increase in maximal systolic arterial blood pressure, and a reduction in ST-segment depression during maximal effort. In addition, a concomitant increase in the number of patients belonging to class I of the NYHA classification (as opposed to classes II and III) and a reduction in the consumption of cardioactive drugs has been reported.26

In subjects with ischemia-induced NYHA II or III cardiac insufficiency, L-carnitine supplementation (1 g three times daily for 120 days), in addition to the usual medications (digitalis, beta-blockers, calcium antagonists, nitrates), resulted in improvements in exercise performance and hemodynamic parameters. Benefits were maintained beyond the L-carnitine supplementation period.27

**Peripheral Vascular Disease**

In a double-blind, crossover study of subjects with peripheral vascular disease, walking distance improved from an average of 174 minutes with placebo to 306 minutes with L-carnitine at a dose of 2 g twice daily for three weeks.28 In healthy subjects, L-carnitine was found to inhibit fatty-acid induced endothelial dysfunction intended to simulate that seen in obesity or type 2 diabetes.29

**Cardiogenic Shock**

L-carnitine supplementation during cardiogenic shock improved metabolic acidosis and survival rate in hospitalized individuals.30,31

**Cardiomyopathy**

Long-term supplementation of L-carnitine (2 g daily) for the treatment of heart failure caused by dilated cardiomyopathy resulted in improvement in survival rate, ejection fraction, Weber classification, maximal time of cardiopulmonary exercise test, peak VO2 consumption, arterial and pulmonary blood pressure, and cardiac output.32,33

**Myocardial Infarction**

Following a recent myocardial infarction (MI), a marked reduction in mortality was observed with 12-month supplementation of 4 g daily L-carnitine (1.2%) when compared to controls (12.5%). Significant improvements were also noted in heart rate and anginal attacks.34 Additional research confirms a benefit in terms of reduced mortality in individuals given L-carnitine following MI.35-37

**Hyperlipidemia**

L-carnitine (2-3 g daily) resulted in improved lipid profiles in individuals with hyperlipidemia, with reductions in total and LDL-cholesterol and increased plasma apolipoprotein A-1 and B levels. Normalization of lipid levels occurred in a substantial number of subjects with continued supplementation for one year.38,39 L-carnitine supplementation (2 g daily) also decreased triglycerides in individuals with essential hypertension.40

L-carnitine (2 g daily) significantly reduced lipoprotein(a) (Lp(a)) levels in 14 of 18 subjects. Reductions in Lp(a) were greater in individuals with more marked elevations prior to supplementation; in a significant number of subjects the reduction of Lp(a) resulted in a return to the normal range.42 Similar results were found in hypercholesterolemic patients newly diagnosed with type 2 diabetes, with significant decreases in Lp(a) levels noted after three and six months of 1 g L-carnitine twice daily. Other measurements taken but not significantly impacted by total cholesterol, triglycerides, and apolipoproteins 43

***Diabetes/Insulin Resistance***

Healthy volunteers and type 2 diabetics received an infusion of L-carnitine or saline, after which plasma glucose and insulin levels were analyzed. Insulin-mediated glucose uptake was significantly higher in both groups receiving L-carnitine compared to the saline groups, indicating improved insulin sensitivity from carnitine.44

A small study found 500-mg intramuscular injections of L-carnitine twice daily for 15 days resulted in improvement in painful diabetic neuropathy.45

**Cancer-Associated Fatigue**

In a small study, 15/18 cancer patients presented with carnitine deficiency, which was postulated to be a significant cause of fatigue in this population.12 Dosage began at 250 mg/day, increasing in increments of 500 mg, to a maximum dose of 3 g daily.

**Chronic Fatigue Syndrome**

Thirty-five patients with chronic fatigue syndrome (CFS) were found to have low free carnitine, total carnitine, and acylcarnitine compared to controls, with a statistically significant correlation between total and free carnitine levels and clinical symptomology.46 In a crossover study, 30 patients with CFS were treated with L-carnitine or amantadine (a drug that provides benefit for fatigue in patients with multiple sclerosis). However, the carnitine supplementation resulted in only one dropout and improvement in 12 of 18 parameters studied.47

***Hepatic Effects***

**Hepatitis**

A study found plasma carnitine levels were significantly lower in children with chronic hepatitis B than in healthy controls. In addition, carnitine levels corresponded inversely to extent of liver fibrosis and inflammation.49

In a single case report, a patient with hyperammonemia associated with a combination of hepatitis C, dialysis, and low free carnitine levels responded to IV L-carnitine. Within three hours of a single 2-g dose, the patient progressed from comatose to normal mental status.50

**Hepatic Encephalopathy from Cirrhosis**

L-carnitine (2 g twice daily) or placebo was administered to 120 patients with hepatic encephalopathy for 60 days. Fasting serum ammonia levels were significantly lower at 30 and 60 days compared to baseline and placebo. Mental function was also significantly improved by L-carnitine, as measured by NCT-A, an accepted psychometric test for mental status in cirrhotic patients. The researchers speculate L-carnitine decreases brain and blood ammonia levels by stimulating ureagenesis.51

***HIV and Immunity***

Daily infusions of L-carnitine (6 g) for four months resulted in an increase in CD4 counts in HIV-positive subjects who were not taking anti-retroviral therapy.52

Administration of L-carnitine (6 g daily for two weeks) to AIDS patients treated with zidovudine (AZT) resulted in improved immunity and a reduction in serum levels of tumor necrosis factor-alpha.53

In another study on HIV patients on AZT and didanosine (DDI), a subgroup was assigned to also receive 6 g L-carnitine daily. Addition of carnitine greatly reduced the negative effects of the drugs, including apoptosis of CD4 and CD8 cells and oxidative stress. No toxicity or decrease in drug effectiveness was noted.54

***Hyperthyroidism***

L-carnitine is believed to be a peripheral antagonist of thyroid hormone activity in some tissues. A randomized, double-blind, placebo-controlled, six-month trial reported both 2- and 4-g daily doses of L-carnitine prevented and reversed hyperthyroidism-related symptoms, including exerting a beneficial effect on bone mineralization.55

***Male Infertility***

Oral administration of L-carnitine (3 g daily for four months) resulted in significant improvements in sperm number, quality, and motility in patients with inadequate sperm.56,57 In another double-blind, crossover trial, 100 infertile males were supplemented with 2 g L-carnitine daily or placebo

for two months, followed by a two-month washout period, and finallytwo months on the opposite treatment. Statistically significant improvements in sperm count and motility were observed in the L-carnitine group.58 The same researchers conducted a second study on 56 infertile males and found the combination of L-carnitine (2 g daily) and acetyl-L-carnitine (1 g daily) led to significant improvement in sperm motility.59

*Renal Failure/Dialysis*

L-carnitine has been extensively studied for patients in renal failure. Supplementation, either orally or intravenously, mitigates some of the disorders associated with dialysis, including renal anemia, cardiac dysfunction, insulin resistance, lipid abnormalities, and oxidative stress.60-63

Treatment for eight months with 1 g L-carnitine three times weekly, administered IV during dialysis sessions, resulted in improved left ventricular ejection fraction.64

The National Kidney Foundation – Kidney Disease Outcome Quality Initiative recommends the use of L-carnitine for the treatment of anemia associated with chronic renal failure.65

*Respiratory Distress in Premature Infants*

A combination of L-carnitine (4 g daily for five days) and betamethasone given to women in the prenatal period reduced both the incidence of respiratory distress syndrome and the mortality of premature newborns.66

L-carnitine supplementation to preterm infants at a dose of 30 mg/kg/day in one study67 and 15 mg/kg/day in a second study68 did not result in significant differences between supplementation and placebo groups in frequency of apnea, weight gain, or length of hospital stays. From the above studies, it appears prenatal supplementation may be of more benefit than newborn supplementation.

A case of siblings presenting with apnea and periodic breathing, along with biochemical defects consistent with a non-specific abnormality of beta-oxidation, suggests L-carnitine might prevent some cases of sudden infant death syndrome.69

*Weight Loss*

In a double-blind study, investigators found no effect of L-carnitine supplementation on weight loss or any variable of body composition measured.70

**NUTRIENT-NUTRIENT INTERACTIONS**

A deficiency of ascorbic acid may decrease endogenous biosynthesis of carnitine.71,72 In guinea pigs, supplementing the diet with ascorbic acid increased carnitine biosynthesis.73

A case report describes normalization of carnitine levels following administration with riboflavin.74 In rats, administration of vitamin B12 increased carnitine biosynthesis.75 Choline supplementation appears to decrease carnitine synthesis.76

**DRUG-NUTRIENT INTERACTIONS**

Anticonvulsant medications, including phenobarbital, valproic acid, phenytoin, and carbamazepine, have a significant lowering effect on carnitine levels.77

The antibiotic pivampicillin negatively impacts carnitine metabolism.78

L-carnitine should be used cautiously, if at all, with pentylenetetrazole, since evidence suggests the combination might exacerbate the side effects of the drug.79

Evidence suggests supplemental L-carnitine might prevent cardiac complications secondary to interleukin-2 immunotherapy in cancer patients80 and cardiac toxicity secondary to adriamycin.81

L-carnitine, when used concurrently with AZT, appears to prevent the drug-induced destruction of myotubes, preserve the structure and volume of mitochondria, and prevent the accumulation of lipids.82

L-carnitine supplementation helps prevent elevation in liver enzymes, as well as the myalgia, weakness, and hypotension induced by isotretinoin.83

Emetine (ipecac) appears to promote carnitine deficiency.84 A case report suggests carnitine deficiency was induced in a patient receiving sulfadiazine and pyrimethamine.85

Evidence also suggests L-carnitine potentiates the anti-arrhythmic effect of propafenone and mexiletine in patients with ischemia.86

## SIDE EFFECTS AND TOXICITY

A variety of mild gastrointestinal symptoms have been reported, including transient nausea and vomiting, abdominal cramps, and diarrhea.

The LD50 in mice is 19.2 g/kg. Mutagenicity data indicate no mutagenicity; however, experiments to determine long-term carcinogenicity have not been conducted.

## DOSAGE

The average therapeutic dose is 1-2 g two to three times daily for a total of 2-6 g daily. No advantage appears to exist in giving an oral dose greater than 2 g at one time, since absorption studies indicate saturation at this dose.

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## REFERENCES

1. Li B, Lloyd ML, Gudjonsson H, et al. The effect of enteral carnitine administration in humans. *Am J Clin Nutr* 1992;55:838-845.

2. Harper P, Elwin CE, Cederblad G. Pharmacokinetics of intravenous and oral bolus doses of L-carnitine in healthy subjects. *Eur J Clin Pharmacol* 1988;35:555-562.

3. Sahajwalla CG, Helton ED, Purich ED, et al. Multiple-dose pharmacokinetics and bioequivalence of L-carnitine 330-mg tablet versus 1-g chewable tablet versus enteral solution in healthy adult male volunteers. *J Pharm Sci* 1995;84:627-633

4. Bach AC, Schirardin H, Sihr MO, Storck D. Free and total carnitine in human serum after oral ingestion of L-carnitine. *Diabete Metab* 1983;9:121-124.

5. Rebouche CJ, Chenard CA. Metabolic fate of dietary carnitine in human adults: identification and quantification of urinary and fecal metabolites. *J Nutr* 1991;121:539-546.

6. Baker H, Frank O, DeAngelis B, Baker ER. Absorption and excretion of L-carnitine during single or multiple dosings in humans. *Int J Vitam Nutr Res* 1993;63:22-26.

7. Jogl G, Hsiao YS, Tong L. Structure and function of carnitine acyltransferases. *Ann N Y Acad Sci* 2004;1033:17-29.

8. Fukao T, Lopaschuk GD, Mitchell GA. Pathways and control of ketone body metabolism: on the fringe of lipid biochemistry. *Prostaglandins Leukot Essent Fatty Acids* 2004;70:243-251.

9. Platell C, Kong SE, McCauley R, Hall JC. Branched-chain amino acids. *J Gastroenterol Hepatol* 2000;15:706-717.

10. Stanley CA. Carnitine deficiency disorders in children. *Ann N Y Acad Sci* 2004;1033:42-51.

11. Evangeliou A, Vlassopoulos D. Carnitine metabolism and deficit – when supplementation is necessary? *Curr Pharm Biotechnol* 2003;4:211-219.

12. Cruciani RA, Dvorkin E, Homel P, et al. L-carnitine supplementation for the treatment of fatigue and depressed mood in cancer patients with carnitine deficiency: a preliminary analysis. *Ann N Y Acad Sci* 2004;1033:168-176.

13. Korkina MB, Korchak GM, Medvedev DI. Clinico-experimental substantiation of the use of carnitine and cobalamin in the treatment of anorexia nervosa. *Zh Nevropatol Psikhiatr Im S S Korsakova* 1989;89:82-87. [Article in Russian]

14. Korkina MV, Korchak GM, Kareva MA. Effects of carnitine and cobamamide on the dynamics of mental work capacity in patients with anorexia nervosa. *Zh Nevropatol Psikhiatr Im S S Korsakova* 1992;92:99-102. [Article in Russian]

15. Giordano C, Perrotti G. Clinical studies of the effects of treatment with a combination of carnitine and cobamamide in infantile anorexia. *Clin Ter* 1979;88:51-60. [Article in Italian]

16. Swart I, Rossouw J, Loots JM, Kruger MC. The effect of L-carnitine supplementation on plasma carnitine levels and various performance parameters of male marathon athletes. *Nutr Res* 1997;17:405-414.

17. Vecchiet L, Di Lisa F, Pieralisi G, et al. Influence of L-carnitine administration on maximal physical exercise. *Eur J Appl Physiol Occup Physiol* 1990;61:486-490.

18. Volek JS, Kraemer WJ, Rubin MR, et al. L-carnitine L-tartrate supplementation favorably affects markers of recovery from exercise stress. *Am J Physiol Endocrinol Metab* 2002;282:E474-E482.

19. Vukovich MD, Costill DL, Fink WJ. Carnitine supplementation: effect on muscle carnitine and glycogen content during exercise. *Med Sci Sports Exerc* 1994;26:1122-1129.

20. Cooper MB, Jones DA, Edwards RH, et al. The effect of marathon running on carnitine metabolism and on some aspects of muscle mitochondrial activities and antioxidant mechanisms. *J Sports Sci* 1986;4:79-87.

21. Colombani P, Wenk C, Kunz I, et al. Effects of L-carnitine supplementation on physical performance and energy metabolism of endurance-trained athletes: a double-blind crossover field study. *Eur J Appl Physiol Occup Physiol* 1996;73:434-439.

22. Kamikawa T, Suzuki Y, Kobayashi A, et al. Effects of L-carnitine on exercise tolerance in patients with stable angina pectoris. *Jpn Heart J* 1984;25:587-597.

23. Canale C, Terrachini V, Biagini A, et al. Bicycle ergometer and echocardiographic study in healthy subjects and patients with angina pectoris after administration of L-carnitine: semiautomatic computerized analysis of M-mode tracing. *Int J Clin Pharmacol Ther Toxicol* 1988;26:221-224.

24. Cherchi A, Lai C, Angelino F, et al. Effects of L-carnitine on exercise tolerance in chronic stable angina: a multicenter, double-blind, randomized, placebo controlled crossover study. *Int J Clin Pharmacol Ther Toxicol* 1985;23:569-572.

25. Iyer RN, Khan AA, Gupta A, et al. L-carnitine moderately improves the exercise tolerance in chronic stable angina. *J Assoc Physicians India* 2000;48:1050-1052.

26. Cacciatore L, Cerio R, Ciarimboli M, et al. The therapeutic effect of L-carnitine in patients with exercise-induced stable angina: a controlled study. *Drugs Exp Clin Res* 1991;17:225-235.

27. Loster H, Miehe K, Punzel M, et al. Prolonged oral L-carnitine substitution increases bicycle ergometer performance in patients with severe, ischemically induced cardiac insufficiency. *Cardiovasc Drugs Ther* 1999;13:537-546.

28. Brevetti G, Chiariello M, Ferulano G, et al. Increases in walking distance in patients with peripheral vascular disease treated with L-carnitine: a double-blind, cross-over study. *Circulation* 1988;77:767-773.

29. Shankar SS, Mirzamohammadi B, Walsh JP, Steinberg HO. L-carnitine may attenuate free fatty acid-induced endothelial dysfunction. *Ann N Y Acad Sci* 2004;1033:189-197.

30. Corbucci GG, Lettieri B. Cardiogenic shock and L-carnitine: clinical data and therapeutic perspectives. *Int J Clin Pharmacol Res* 1991;11:283-293.

31. Corbucci GG, Loche F. L-carnitine in cardiogenic shock therapy: pharmacodynamic aspects and clinical data. *Int J Clin Pharmacol Res* 1993;13:87-91.

32. Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. *Am Heart J* 2000;139:S120-S123.

33. Gurlek A, Tutar E, Akcil E, et al. The effects of L-carnitine treatment on left ventricular function and erythrocyte superoxide dismutase activity in patients with ischemic cardiomyopathy. *Eur J Heart Fail* 2000;2:189-193.

34. Davini P, Bigalli A, Lamanna F, Boem A. Controlled study on L-carnitine therapeutic efficacy in post-infarction. *Drugs Exp Clin Res* 1992;18:355-365.

35. De Pasquale B, Righetti G, Menotti A. L-carnitine for the treatment of acute myocardial infarct. *Cardiologia* 1990;35:591-596.

36. Singh RB, Niaz MA, Agarwal P, et al. A randomised, double-blind, placebo-controlled trial of L-carnitine in suspected acute myocardial infarction. *Postgrad Med J* 1996;72:45-50.

37. Iliceto S, Scrutinio D, Bruzzi P, et al. 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;26:380-387.

38. Stefanutti C, Vivenzio A, Lucani G, et al. Effect of L-carnitine on plasma lipoprotein fatty acids pattern in patients with primary hyperlipoproteinemia. *Clin Ter* 1998;149:115-119.

39. Fernandez C, Proto C. L-carnitine in the treatment of chronic myocardial ischemia. An analysis of 3 multicenter studies and a bibliographic review. *Clin Ter* 1992;140:353-377.

40. Digiesi V, Cantini F, Bisi G, et al. L-carnitine adjuvant therapy in essential hypertension. *Clin Ter* 1994;144:391-395.

41. Kosan C, Sever L, Arisoy N, et al. Carnitine supplementation improves apolipoprotein B levels in pediatric peritoneal dialysis patients. *Pediatr Nephrol* 2003;18:1184-1188.

42. Sirtori CR, Calabresi L, Ferrara S, et al. L-carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a). *Nutr Metab Cardiovasc Dis* 2000;10:247-251.

43. Derosa G, Cicero AF, Gaddi A, et al. The effect of L-carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. *Clin Ther* 2003;25:1429-1439.

44. Mingrone G, Greco AV, Capristo E, et al. L-carnitine improves glucose disposal in type 2 diabetic patients. *J Am Coll Nutr* 1999;18:77-82.

45. Cakir N, Yetkin I, Karakoc A, et al. L-carnitine in the treatment of painful diabetic neuropathy and its effect on plasma beta-endorphin levels. *Curr Ther Res Clin Exp* 2000;61:871-876.

46. Plioplys AV, Plioplys S. Serum levels of carnitine in chronic fatigue syndrome: clinical correlates. *Neuropsychobiology* 1995;32:132-138.

47. Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology* 1997;35:16-23.

48. Sachan DS, Rhew TH, Ruark RA. Ameliorating effects of carnitine and its precursors on alcohol-induced fatty liver. *Am J Clin Nutr* 1984;39:738-744.

49. Selimoglu MA, Yagci RV. Plasma and liver carnitine levels of children with chronic hepatitis B. *J Clin Gastroenterol* 2004;38:130-133.

50. DaVanzo WJ, Ullian ME. L-carnitine administration reverses acute mental status changes in a chronic hemodialysis patient with hepatitis C infection. *Clin Nephrol* 2002;57:402-405.

51. Malaguarnera M, Pistone G, Astuto M, et al. L-carnitine in the treatment of mild or moderate hepatic encephalopathy. *Dig Dis* 2003;21:271-275.

52. Moretti S, Alesse E, Di Marzio L, et al. Effect of L-carnitine on human immunodeficiency virus-1 infection-associated apoptosis: a pilot study. *Blood* 1998;91:3817-3824.

53. De Simone C, Tzantzoglou S, Famularo G, et al. High dose L-carnitine improves immunologic and metabolic parameters in AIDS patients. *Immunopharmacol Immunotoxicol* 1993;15:1-12.

54. Moretti S, Famularo G, Marcellini S, et al. L-carnitine reduces lymphocyte apoptosis and oxidant stress in HIV-1-infected subjects treated with zidovudine and didanosine. *Antioxid Redox Signal* 2002;4:391-403.

55. Benvenga S, Ruggeri RM, Russo A, et al. 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;86:3579-3594.

56. Costa M, Canale D, Filicori M, et al. L-carnitine in idiopathic asthenozoospermia: a multicenter study. Italian Study Group on Carnitine and Male Infertility. *Andrologia* 1994;26:155-159.

57. Vitali G, Parente R, Melotti C. Carnitine supplementation in human idiopathic asthenospermia: clinical results. *Drugs Exp Clin Res* 1995;21:157-159.

58. Lenzi A, Lombardo F, Sgro P, et al. Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. *Fertil Steril* 2003;79:292-300.

59. Lenzi A, Sgro P, Salacone P, et al. A placebo-controlled double-blind randomized trial of the use of combined L-carnitine and L-acetyl-carnitine treatment in men with asthenozoospermia. *Fertil Steril* 2004;81:1578-1584.

60. Gunal AI, Celiker H, Donder E, Gunal SY. The effect of L-carnitine on insulin resistance in hemodialysed patients with chronic renal failure. *J Nephrol* 1999;12:38-40.

61. Vesela E, Racek J, Trefil L, et al. Effect of L-carnitine supplementation in hemodialysis patients. *Nephron* 2001;88:218-223.

62. Matsumoto Y, Amano I, Hirose S, et al. Effects of L-carnitine supplementation on renal anemia in poor responders to erythropoietin. *Blood Purif* 2001;19:24-32.

63. Elisaf M, Bairaktari E, Katopodis K, et al. Effect of L-carnitine supplementation on lipid parameters in hemodialysis patients. *Am J Nephrol* 1998;18:416-421.

64. Romagnoli GF, Naso A, Carraro G, Lidestri V. Beneficial effects of L-carnitine in dialysis patients with impaired left ventricular function: an observational study. *Curr Med Res Opin* 2002;18:172-175.

65. Golper TA, Goral S, Becker BN, Langman CB. L-carnitine treatment of anemia. *Am J Kidney Dis* 2003;41:S27-S34.

66. Kurz C, Arbeiter K, Obermair A, et al. L-carnitine-betamethasone combination therapy versus betamethasone therapy alone in prevention of respiratory distress syndrome. *Z Geburtshilfe Perinatol* 1993;197:215-219. [Article in German]

67. O□Donnell J, Finer NN, Rich W, et al. Role of L-carnitine in apnea of prematurity: a randomized, controlled trial. *Pediatrics* 2002;109:622-626.

68. Whitfield J, Smith T, Sollohub H, et al. Clinical effects of L-carnitine supplementation on apnea and growth in very low birth weight infants. *Pediatrics* 2003;111:477-482.

69. Iafolla AK, Browning IB 3rd, Roe CR. Familial infantile apnea and immature beta oxidation. *Pediatr Pulmonol* 1995;20:167-171.

70. Villani RG, Gannon J, Self M, Rich PA. L-Carnitine supplementation combined with aerobic training does not promote weight loss in moderately obese women. *Int J Sport Nutr Exerc Metab* 2000;10:199-207.

71. Johnston CS, Solomon RE, Corte C. Vitamin C depletion is associated with alterations in blood histamine and plasma free carnitine in adults. *J Am Coll Nutr* 1996;15:586-591.

72. Ha TY, Otsuka M, Arakawa N. The effect of graded doses of ascorbic acid on the tissue carnitine and plasma lipid concentrations. *J Nutr Sci Vitaminol (Tokyo)* 1990;36:227-234.

73. Otsuka M, Matsuzawa M, Ha TY, Arakawa N. Contribution of a high dose of L-ascorbic acid to carnitine synthesis in guinea pigs fed high-fat diets. *J Nutr Sci Vitaminol (Tokyo)* 1999;45:163-171.

74. Triggs WJ, Roe CR, Rhead WJ, et al. Neuropsychiatric manifestations of defect in mitochondrial beta oxidation response to riboflavin. *J Neurol Neurosurg Psychiatry* 1992;55:209-211.

75. Podlepa EM, Gessler NN, Bykhovskii VIa. The effect of methylation on the carnitine synthesis. *Prikl Biokhim Mikrobiol* 1990;26:179-183. [Article in Russian]

76. Dodson WL, Sachan DS. Choline supplementation reduces urinary carnitine excretion in humans. *Am J Clin Nutr* 1996;63:904-910.

77. Hug G, McGraw CA, Bates SR, Landrigan EA. Reduction of serum carnitine concentrations during anticonvulsant therapy with phenobarbital, valproic

acid, phenytoin, and carbamazepine in children. *J Pediatr* 1991;119:799-802.

78. Melegh B, Pap M, Molnar D, et al. Carnitine administration ameliorates the changes in energy metabolism caused by short-term pivampicillin medication. *Eur J Pediatr* 1997;156:795-799.

79. Herink J. Enhancing effect of L-carnitine on some abnormal signs induced by pentylenetetrazol. *Acta Medica (Hradec Kralove)* 1996;39:63-66.

80. Lissoni P, Galli MA, Tancini G, Barni S. Prevention by L-carnitine of interleukin-2 related cardiac toxicity during cancer immunotherapy. *Tumori* 1993;79:202-204.

81. Kawasaki N, Lee JD, Shimizu H, Ueda T. Long-term L-carnitine treatment prolongs the survival in rats with adriamycin-induced heart failure. *J Card Fail* 1996;2:293-299.

82. Semino-Mora MC, Leon-Monzon ME, Dalakas MC. Effect of L-carnitine on the zidovudine-induced destruction of human myotubes. Part I: L-carnitine prevents the myotoxicity of AZT *in vitro*. *Lab Invest* 1994;71:102-112.

83. Georgala S, Schulpis KH, Georgala C, Michas T. L-carnitine supplementation in patients with cystic acne on isotretinoin therapy. *J Eur Acad Dermatol Venereol* 1999;13:205-209.

84. Kuntzer T, Reichmann H, Bogousslavsky J, Regli F. Emetine-induced myopathy and carnitine deficiency. *J Neurol* 1990;237:495-496.

85. Sekas G, Paul HS. Hyperammonemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med* 1993;95:112-113.

86. Mondillo S, Faglia S, D□Aprile N, et al. Therapy of arrhythmia induced by myocardial ischemia. Association of L-carnitine, propafenone and mexiletine. *Clin Ter* 1995;146:769-774.



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