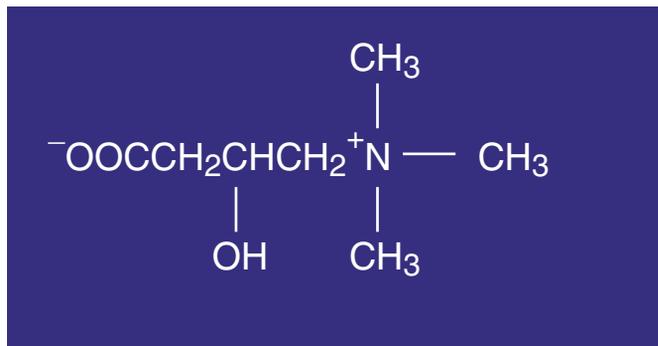


Chemical Structure of L-Carnitine



L-Carnitine

Introduction

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 percent^{2,3} 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

Deficiency can result in cardiomyopathy, congestive heart failure, encephalopathy, hepatomegaly, impaired growth and development in infants, and neuromuscular disorders.

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 smooth muscle.

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

In a study of pediatric patients on dialysis, oral L-carnitine at 50 mg/kg/day for 30 days resulted in significant decrease in apolipoprotein B levels, with no changes in other lipid parameters.⁴¹

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 L-carnitine were body mass index, fasting glucose, postprandial glucose, glycosylated hemoglobin, LDL- and HDL-cholesterol, total cholesterol, triglycerides, and apolipoproteins A-1 and B.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

Fatigue

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. After one week of supplementation, patients experienced significant improvement in fatigue, depression, and sleep quality.

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). Each substance was administered for two months with a two-week washout period. Half of the patients dropped out of the study, mainly due to intolerance of the amantadine. However, the carnitine supplementation resulted in only one dropout and improvement in 12 of 18 parameters studied.⁴⁷

Hepatic Effects

Fatty Liver

L-carnitine ameliorates ethanol-induced fatty liver in animals;⁴⁸ however, it has not been investigated in humans for this condition.

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 finally

two 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.

Warnings and Contraindications

L-carnitine is listed as pregnancy category B, indicating animal studies have revealed no harm to the fetus but that no adequate studies in pregnant women have been conducted. L-carnitine has been given to pregnant women late in pregnancy with resulting positive outcomes.

The racemic mixture (D,L-carnitine) should be avoided. D-carnitine is not biologically active and might interfere with the proper utilization of the L isomer. In uremic patients, use of the racemic mixture has been correlated with myasthenia-like symptoms in some individuals.

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