L-Carnitine: Therapeutic Applications of a Conditionally-Essential Amino Acid.

by Gregory S. Kelly, N.D.

Abstract

A trimethylated amino acid roughly similar in structure to choline, 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. Mitochondrial fatty acid oxidation is the primary fuel source in heart and skeletal muscle, pointing to the relative importance of this nutrient for proper function in these tissues. Although L-carnitine deficiency is an infrequent problem in a healthy, well-nourished population consuming adequate protein, many individuals within the population appear to be somewhere along a continuum, characterized by mild deficiency at one extreme, and tissue pathology at the other. Conditions which seem to benefit from exogenous supplementation of L-carnitine include anorexia, chronic fatigue, coronary vascular disease, diphtheria, hypoglycemia, male infertility, muscular myopathies, and Rett syndrome. In addition, preterm infants, dialysis patients, and HIV positive individuals seem to be prone to a deficiency of L-carnitine, and benefit from supplementation. Although available data on L-carnitine as an ergogenic aid is not compelling, under some experimental conditions pretreatment has favored aerobic processes and resulted in improved endurance performance.
Altern Med Rev 1998;3(5):345-360.

Introduction

Although L-carnitine was originally discovered in 1905, its crucial role in metabolism was not elucidated until 1955, and primary L-carnitine deficiency was not described until 1972. The most significant source of L-carnitine in human nutrition is meat, although humans are also capable of synthesizing L-carnitine from dietary amino acids. It has generally been assumed that a well-balanced diet contains both a significant amount of carnitine, and all of the essential amino acids and micronutrients needed for carnitine biosynthesis; however, increasingly investigators have identified conditions and individuals for which L-carnitine appears to be a conditionally-essential nutrient. Thus, although L-carnitine deficiency is an infrequent problem in a healthy, well-nourished population consuming adequate protein, many individuals within the population appear to be somewhere along a continuum characterized by mild deficiency at one extreme and tissue pathology at the other.

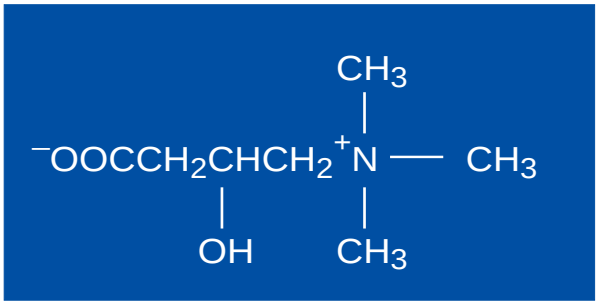
Gregory S. Kelly, N.D.—Associate Editor, Alternative Medicine Review; Private Practice, Greenwich, CT.
Correspondence address: 56 Lafayette Place, Suite C, Greenwich, CT 06830.

Biochemistry

A trimethylated amino acid similar in structure to choline, carnitine (see Figure 1) 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. Mitochondrial fatty acid oxidation is the primary fuel source in heart and skeletal muscle, pointing to the relative importance of this nutrient for proper function in these tissues.

Carnitine synthesis begins with methylation of the amino acid L-lysine by S-adenosylmethionine (SAM). Methionine, magnesium, ascorbic acid, iron, P5P, and niacin, along with the cofactors responsible for regenerating SAM from homocysteine (5-methyltetrahydrofolate, methylcobalamin, and betaine) are all required for endogenous carnitine synthesis (see Figure 2).

Figure 1. Chemical structure of carnitine.



In order to form L-carnitine from lysine, three consecutive methylation reactions are required, with SAM acting as the methyl donor, resulting in the formation of trimethyllysine. Trimethyllysine is enzymatically transformed into hydroxytrimethyllysine in a reaction requiring alpha-ketoglutarate, oxygen, ascorbic acid and iron. The next step in the endogenous synthesis of L-carnitine requires pyridoxal 5'-phosphate (vitamin B6) and results in the formation of trimethylaminobutyraldehyde. Trimethylaminobutyrate (or gamma-butyrobetaine) is then formed in a reaction requiring NADH (vitamin B3 dependent). The gamma-butyrobetaine is finally hydroxylated into carnitine in a reaction which again requires alpha-ketoglutarate, oxygen, ascorbic acid and iron.

A pivotal enzyme in carnitine synthesis, betaine aldehyde dehydrogenase is the same enzyme responsible for synthesis of betaine from choline. Two recent studies suggest this enzyme has a preference for the choline-betaine conversion, since choline supplementation appeared to decrease carnitine synthesis.[1, 2]

Pharmacokinetics

The pharmacokinetic properties of an orally administered dose of L-carnitine have not been unequivocally described in the literature, and might have considerable variability depending upon the relative carnitine stores of an individual. Evidence indicates L-carnitine is absorbed in the intestine by a combination of active transport and passive diffusion.[3]

There appears to be no significant advantage of supplementing an oral dose of L-carnitine in amounts greater than 2 g, since pharmacokinetic studies suggest mucosal absorption of carnitine is saturated at about a 2 g dose.[4] Maximum blood concentrations are reached approximately 3.5 hours following an oral dose, with a half-life of about 15 hours. Elimination of carnitine occurs primarily through the kidneys.[5]

Although evidence suggests dietary carnitine is not totally absorbed and is in part degraded in the gastrointestinal tract of humans, there is some disagreement on the actual bioavailability of an oral dose. Rebouche and Chenard gave a radio-labeled dose of

L-carnitine orally with a meal to subjects who had been adapted to a low-carnitine diet or a high-carnitine diet in order to determine the metabolic fate of dietary carnitine in humans. Their results suggested an oral bioavailability of 54 to 87 percent depending upon the dose of L-carnitine consumed.[6] Bach et al also presented evidence suggesting relatively high absorption of L-carnitine. Following a 2 g oral dose of L-carnitine, they reported an increase in total blood carnitine levels of about 57 percent and in the free form of L-carnitine of about 81 percent.[5]

In contrast to these observations, several researchers have suggested much lower bioavailability. Sahajwalla et al indicated an absolute bioavailability of approximately 18 percent in healthy volunteers.[7] Harper et al similarly reported a relatively low oral bioavailability. Following a 2 g dose they estimated bioavailability to be approximately 16 percent.[4]

Baker et al evaluated the changes in free and acylcarnitine activity in plasma, whole blood, red blood cells, and urine following oral doses of L-carnitine (a single dose of 500 mg or 2500 mg, or by ingestion of a daily dose of 2500 mg for 10 days). Increased levels of free carnitine were observed in the urine following all dosage regimens, while a single or consistent daily dose of 2500 mg of carnitine increased free and acylcarnitine in plasma, whole blood and urine to the greatest degrees. However, irrespective of dosage, these researchers observed no significant change in red blood cell carnitine levels, 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.[8] It is not known whether similar findings would be observed in conditions characterized by functional deficiency; however, based upon consistent clinical observations, it is likely some degree of tissue repletion occurs following an oral dose.

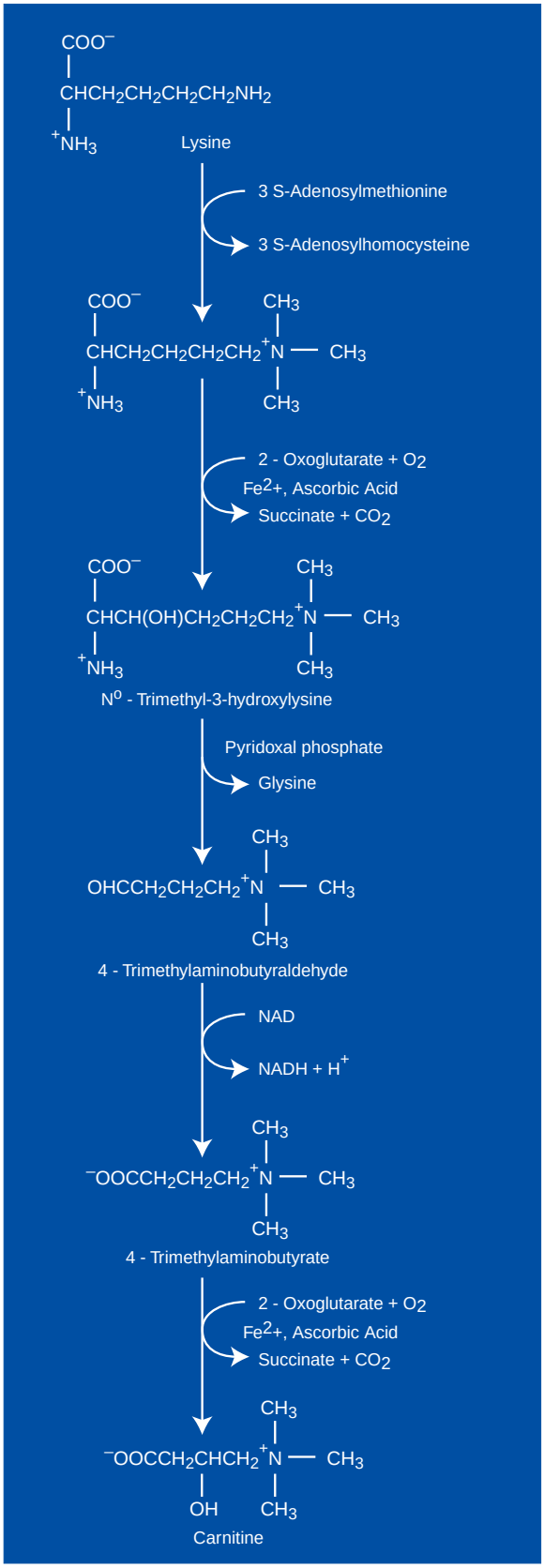
Deficiency

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. Carnitine levels of vegetarians are reported to be below normal. Infants fed carnitine-free formulas are also in jeopardy of deficiency, since endogenous synthesis is not adequate to cover systemic needs during the first few days of the postnatal period. 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. Secondary carnitine deficiency is not as rare and is most commonly associated with dialysis, although intestinal resection, severe infections, and liver disease can also induce a secondary deficiency. Other symptoms of a chronic carnitine deficiency can include hypoglycemia, progressive myasthenia, hypotonia, or lethargy. Because of carnitine's role in fatty acid metabolism, elevated triglycerides as a lab finding might, among a variety of possibilities, be indicative of a relative deficiency of carnitine. Pathological manifestations of chronic deficiency include accumulation of neutral lipid within skeletal muscle, heart tissue and liver, a disruption of muscle fibers, and an accumulation of large aggregates of mitochondria within the skeletal and smooth muscle. Because of these changes, a deficiency can result in cardiomyopathy, congestive heart failure, encephalopathy, hepatomegaly, impaired growth and development in infants, and neuromuscular disorders.

Diet and Nutritional Interactions

It is assumed a diet adequate in protein will supply enough exogenous, and promote any additional endogenous, synthesis

Figure 2. Synthesis of carnitine.



needed to supply an individual's requirements for L-carnitine. However, since L-carnitine is found primarily in animal proteins, with red meat regarded as the richest source, it is theoretically possible to consume a high protein diet consisting of beans, legumes, or egg whites and still promote a relative deficiency.

Since a vegetarian diet is very low in exogenous carnitine, and is potentially low in some of the substrates required for carnitine synthesis, there is some concern that following a strict vegetarian diet might produce a carnitine deficiency in some individuals. A case report in the literature seems to lend credence to this possibility. In this report, a 12-year-old consuming a vegetarian diet had recurrent episodes of vomiting, lethargy, and hypoglycemia dating back 11 years. Investigations revealed a systemic carnitine deficiency that, when corrected, promptly improved his condition.[9]

Results indicate the macronutrient composition of a diet, other than protein content, can influence carnitine metabolism. In seven healthy men receiving the same amount of dietary carnitine, plasma free carnitine rose significantly in individuals following a high-fat, low-carbohydrate diet, while no change in carnitine level was observed in individuals on a high-carbohydrate, low-fat diet. Renal excretion of carnitine increased only on the higher fat diet as well. This evidence suggests a high-fat, low-carbohydrate diet might be capable of boosting endogenous synthesis of carnitine and its metabolites.[10] Coupled with this observation is the clinical finding that some individuals consuming a high carbohydrate diet for prolonged periods of time present with vague symptoms of fatigue and hypoglycemia, symptoms which can be indicative of a relative carnitine deficiency. In these individuals it might be prudent to assess carnitine status.

Although medium-chain triglycerides (MCTs) have generally been assumed to be

utilized as an energy substrate independently of carnitine, Rossle et al have shown the administration of MCTs does impact plasma concentrations of free carnitine and acylcarnitines, suggesting MCTs might not be metabolized independently of carnitine.[11] Since carnitine deficiency can also impair ketogenesis, individuals consuming a ketogenic diet high in MCTs should be monitored for signs or symptoms suggestive of carnitine deficiency.

Davis et al have shown that very low calorie diets (between 420-600 kcal/day) can have a negative effect on both plasma and urinary carnitine levels. Although plasma short-chain acylcarnitine esters increased and free carnitine declined significantly, protein consumption appeared to exert a sparing effect on carnitine since individuals consuming a preponderance of calories as meat/fish/poultry maintained significantly higher levels of plasma total carnitine.[12]

Ascorbic acid is required for the biosynthesis of L-carnitine, so it is not surprising to find a deficiency of ascorbic acid will decrease endogenous biosynthesis of carnitine.[13,14] Experimental evidence suggests some forms of vitamin B12 affect carnitine synthesis. In rats, administration of methylcobalamin, cyanocobalamin, and hydroxycobalamin have been shown to stimulate carnitine synthesis. This is probably due to the use of vitamin B12 in the re-methylation of homocysteine to methionine, since biochemically, SAM must donate methyl groups to complete the endogenous generation of carnitine from lysine.[15] Although evidence is currently unavailable, it is possible deficiencies in other nutrients required for optimal levels of SAM, such as methionine, magnesium, folic acid, and betaine, might impair endogenous synthesis of L-carnitine.

Although the precise role of riboflavin (B2) in carnitine metabolism has not been elucidated, a case report suggests this vitamin might be an important component in optimizing carnitine levels in some individuals. In the report, Triggs et al describe a 29-year-old female with severe nausea and vomiting of pregnancy, migraines, psychiatric illness, non-epileptic seizures, and valproate-induced coma. Treatment with riboflavin normalized her plasma free carnitine level, and had a beneficial impact on her headaches and behavior.[16]

Since adequate dietary lysine is required as a substrate for carnitine synthesis, a deficiency of this amino acid or the other cofactors—iron, vitamin C, B6, niacin—might also compromise carnitine status.

Due to the choline-betaine pathway sharing an enzyme with the lysine to carnitine pathway, which was mentioned earlier,[1,2] choline supplementation might decrease carnitine synthesis; therefore, it might be of greater benefit to supplement with betaine rather than its precursors, choline or phosphatidylcholine. In individuals consuming high amounts of choline, phosphatidylcholine, or lecithin (a rich source of phosphatidylcholine), additional supplementation of L-carnitine or an assessment of L-carnitine status might be warranted.

Drug Interactions

Anticonvulsant therapy, including phenobarbital, valproic acid, phenytoin, and carbamazepine, has a significant lowering effect on carnitine levels.[17] Pivampicillin treatment is also known to negatively impact carnitine metabolism.[18]

L-carnitine should be used cautiously if at all with pentylenetetrazol, a respiratory stimulant drug, since evidence suggests the combination might enhance the side-effects of the drug.[19]

Evidence suggests L-carnitine might prevent the cardiac complications secondary to interleukin-2 immunotherapy in cancer patients.[20] Experimental evidence also suggests L-carnitine might be able to prevent cardiac toxicity secondary to the administration of

adriamycin.[21] L-Carnitine, when used concurrently with zidovudine (AZT), appears to prevent the AZT-induced destruction of myotubules, preserve the structure and volume of mitochondria, and prevent the accumulation of lipids.[22]

Anorexia

In patients with anorexia nervosa, carnitine and adenosylcobalamin accelerated body weight gain and normalization of gastrointestinal function. Latent fatigue was reported to disappear and mental performance increase under this treatment regimen.[23] Korkina et al reported the combined use of carnitine and adenosylcobalamin eliminated fluctuations in the work rate and improved the scope and productivity of intellectual work in patients with anorexia nervosa in the stage of cachexia, although latent fatigue in the population studied was not fully removed.[24]

Children with infantile anorexia also appear to respond well to a combination of carnitine and adenosylcobalamin. One group of children was given 2000 mcg adenosylcobalamin and 1000 mg carnitine, while the other group was given cyproheptadine, an anti-histamine used to stimulate appetite. Results of adenosylcobalamin and carnitine treatment were judged good by the authors, were comparable to the effects of the pharmaceutical agent, and were produced with no side-effects.[25]

Athletic Performance

Carnitine is promoted as a supplement needed to improve the body's ability to use stored fat as fuel. Supplementation purportedly enhances lipid oxidation, increases VO2 max, and decreases plasma lactate accumulation during exercise.

Several investigators have suggested L-carnitine supplementation might benefit athletes. Swart et al investigated the effect of giving 2 grams/day of L-carnitine for 6 weeks to seven male marathon athletes. They reported a 5.68 percent increase in running speed, and decreased average oxygen consumption and heart rate in a treadmill test following supplementation. The authors suggest that in order for carnitine to be effective as an ergogenic aid the athlete must have a relative shortage of endogenous carnitine to begin with and an adequate supply of lipids available as fuel, which will shift metabolism toward the utilization of fats as an energy source. Because the average free and total plasma carnitine levels were below the normal ranges prior to supplementation, the L-carnitine might have helped to overcome a relative endogenous deficiency for the participants involved in this study.[26]

Siliprandi et al, in a small double-blind cross-over study of ten moderately-trained male subjects, gave either 2 grams of L-carnitine or placebo orally one hour prior to exercise. Supplementation with L-carnitine induced a significant post-exercise decrease of plasma lactate and pyruvate and a concurrent increase of acetylcarnitine.[27] Vecchiet et al randomly gave 2 grams of L-carnitine or a placebo to subjects one hour before they began exercise. At the maximal exercise intensity, treatment with L-carnitine increased both maximal oxygen uptake and power output. The authors also reported, at similar, non-maximal, exercise intensities, participants receiving L-carnitine had reduced oxygen uptake, carbon dioxide production, pulmonary ventilation, and plasma lactate.[28]

While some of the results with L-carnitine supplementation have been promising, not all research is in agreement. Heinonen, in his review of carnitine supplementation and physical exercise, concluded that its impact on performance in athletes is equivocal: it does not enhance fatty acid oxidation, spare glycogen or postpone fatigue during exercise; it does not stimulate pyruvate dehydrogenase activity; and it does not reduce body fat or help with weight loss.[29]

Vukovich et al found chronic carnitine supplementation (6 g/day) resulted in no differences in VO2, respiratory exchange ratio, heart rate, or carbohydrate and fat utilization. They also reported muscle carnitine concentration at rest was unaffected by supplementation.[30] Barnett et al similarly reported carnitine supplementation of 4 g/day for 14 days, while effective at increasing plasma total acid soluble and free carnitine concentrations, had no significant effect on muscle carnitine concentrations.[31] Cooper et al found loading of athletes with L-carnitine for 10 days prior to a marathon, while abolishing the exercise-induced fall in plasma free carnitine and increasing the production of acetylcarnitine, resulted in no detectable improvement in performance.[32]

Colambani et al investigated the effects of L-carnitine supplementation on metabolism and performance of endurance-trained athletes during and after a marathon run. In a double-blind cross-over field study, seven male subjects received two grams of L-carnitine two hours before the start of a marathon run and again after 20 km of running. Although the administration of L-carnitine was associated with a significant increase in the plasma concentration of all analyzed carnitine fractions, significant changes in running time, plasma concentrations of carbohydrate metabolites (glucose, lactate, and pyruvate), as well as fat metabolites (free fatty acids, glycerol, and beta-hydroxybutyrate), hormones (insulin, glucagon, and cortisol), and enzyme activities (creatine kinase and lactate dehydrogenase) were not observed.[33]

Although available data on L-carnitine as an ergogenic aid is not compelling, under some experimental conditions pretreatment has favored aerobic processes. It is possible L-carnitine might only exert a beneficial effect when there are actual deficiencies. Availability of fat as a substrate for fuel might also impact the ability of carnitine to act as an ergogenic aid. Supplementation of 2 grams one hour prior to intensive exercise might provide some benefits; however, based on the mixed results and the cost of the supplement, long term administration of L-carnitine as an ergogenic aid is difficult to justify.

Chronic Fatigue Syndrome and Mitochondrial Myopathy

Researchers investigating the oral administration of L-carnitine as a potential treatment for chronic fatigue syndrome observed clinical improvement in 12 of 18 patients. They also reported the trend for the greatest improvement occurred between weeks four and eight of treatment. One patient was unable to complete the trial due to the development of diarrhea.[34]

Campos et al found plasma carnitine "insufficiency," (defined as plasma esterified carnitine to free carnitine ratio above 0.25) in 21 of 48 (43.8%) patients with mitochondrial myopathy. They proceeded to treat the patients classified as "insufficient" with L-carnitine (50-200 mg/kg four times daily) and observed improvements in muscle weakness in 19 of 20 patients, failure to thrive in 4 of 8, encephalopathy in 1 of 9, and cardiomyopathy in 8 of 8 patients.[35]

Diphtheria

Ramos et al studied the effect of carnitine supplementation in patients with diphtheria. In addition to standard treatment for diphtheria, they divided 625 children into two groups. Three hundred twenty-seven patients received DL-carnitine (100 mg/kg/day in two divided doses orally for four days) while the remaining patients served as controls. The patients who received carnitine had a significant reduction in both the incidence and mortality of diphtheria-induced myocarditis.[36]

Heart Disease (General)

Although several studies have indicated limited or no benefit of L-carnitine administration during coronary bypass surgery, the preponderance of evidence currently available suggests a beneficial effect of this nutritional supplement in reducing risk factors such as lipid levels and blood pressure, improving physiological function, and impacting the clinical outcomes in coronary conditions such as angina, cardiomyopathy, and congestive heart failure.

Angina, Ischemia and Peripheral Vascular Disease

Since myocardial carnitine content declines within 15-30 minutes of ischemia, it is not surprising to find administration of L-carnitine offers tangible therapeutic benefits for individuals with angina. Kamikawa et al suggest that L-carnitine (900 mg daily given orally) might moderately improve exercise tolerance in patients with stable angina. Their results indicate the benefits of supplementation appear to increase over time, with a longer supplementation period typically resulting in a prolonged angina-free period during exercise. Although several individuals in this trial were free from angina following carnitine supplementation, the majority of patients were only able to extend their angina-free exercise time by about 10 percent . They also observed significantly less ST segment depression during the same exercise load after 12 weeks of oral administration of L-carnitine.[37] Canale et al also found less ST segment depression following oral supplementation of 3 g of L-carnitine daily for 30 days in individuals with angina.[38]

In a multicenter, double-blind, randomized, placebo-controlled cross-over trial of L-carnitine in stable effort-induced angina, twenty-two percent of the patients given L-carnitine became free of angina, compared with 9 percent in the group given placebo. Overall their results indicated increased exercise tolerance and reduced ECG indices of ischemia following supplementation.[39] An investigation of L-carnitine supplementation (2 g/day) in 100 randomly selected patients with exercise-induced stable angina over a six-month period resulted in a reduction in the number of premature ventricular contractions at rest, an improvement in exercise tolerance, an increase in maximal systolic arterial blood pressure, and a reduction in ST-segment depression during maximal effort. In all patients L-carnitine was given in addition to the already instituted therapy. A concomitant increase in the number of patients belonging to class I of the NYHA classification and a reduction in the consumption of cardioactive drugs was also observed in the subjects receiving L-carnitine.[40] In an analysis of three multicenter trials, Fernandez and Proto found a net reduction in the rate of anginal episodes and use of nitrates in patients treated with 2 g/day of L-carnitine. They also noted a normalization of plasma cholesterol levels in 455 of 737 individuals with previously abnormally high levels subsequent to one year of supplementation with L-carnitine.[41]

A double-blind, cross-over study evaluating the effects of L-carnitine supplementation (2 g twice daily for 3 weeks) in patients with peripheral vascular disease revealed an increase in walking distance from an average of 174 minutes with placebo to 306 minutes with L-carnitine. These researchers also observed a more rapid recovery to the resting value of the lactate/pyruvate ratio in individuals receiving L-carnitine.[42]

Evidence also suggests that L-carnitine potentiates the anti-arrhythmic effect of propafenone and mexiletine in patients with ischemia.[43]

Cardiogenic Shock

Corbucci and Lettieri observed a protective effect of L-carnitine supplementation during cardiogenic shock. They suggested L-carnitine might provide its benefit by mitigating against metabolic acidosis, protecting against the destruction of enzymes, and minimizing cellular oxidative damage.[44] In a follow-up study, a similar positive trend was noted in terms of survival rate in individuals administered L-carnitine for cardiogenic shock.[45]

Cardiomyopathy

Ino et al have suggested "the determination of plasma carnitine concentrations and fatty acid metabolism by-products should be performed in all patients with cardiomyopathy of unknown etiology because carnitine supplementation may lead to improvement." This statement was a result of their findings in children with hypertrophic and dilated cardiomyopathy associated with abnormal carnitine metabolism. Their results indicate a relatively high percentage of these children responded favorably to prolonged administration of L-carnitine.[46]

It is suggested that a synergistic protective action might be obtained with a combination of beta-blocking agents and L-carnitine in the treatment of hypertrophic cardiomyopathy. They presented a case of a 52-year-old male with dilated cardiomyopathy who responded successfully to treatment with the combination of L-carnitine and propranolol, resulting in restored cardiac function and a 50-percent reduction in mitral EPSS (E Point Septal Separation) from 20 to 10 mm.[47]

Congestive Heart Failure

The therapeutic efficacy of L-carnitine in subjects suffering from heart failure has been repeatedly demonstrated. Davini et al concluded "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." This conclusion was based upon a controlled study conducted on 160 patients discharged from hospitalization following the diagnosis of a recent myocardial infarction. L-carnitine (4 g/day orally) was administered to 81 of the patients for 12 months. Patients in both the control and treatment groups were also maintained on appropriate pharmacological treatment. Although improvements in heart rate, systolic and diastolic arterial pressure, and lipid parameters, as well as a decrease in anginal attacks, rhythm disorders, and clinical signs of impaired myocardial contractility were observed, the most significant finding of their study was the marked reduction in mortality associated with supplementation of L-carnitine (1.2%) when compared to controls (12.5%).[48]

Others have also reported on the treatment of acute myocardial infarction. In 49 patients administered L-carnitine, their results predicted a worse prognosis for individuals who do not receive supplemental L-carnitine, since their pilot study clearly showed a significant benefit in terms of reduced mortality in the individuals given L-carnitine.[49]

Singh et al have similarly reported a therapeutic benefit of L-carnitine supplementation following suspected acute myocardial infarction. In a randomized, double-blind placebo-controlled trial, supplementation of L-carnitine (2 g/day orally for 28 days) reduced the mean infarct size as assessed by cardiac enzymes, improved QRS-scores, and decreased the number of individuals who suffered from cardiac events, including cardiac deaths and nonfatal infarction, from 26 percent in the placebo group to 15.6 percent in the carnitine group.[50]

In a randomized, double-blind, placebo-controlled, multi-center trial, 472 patients

with a first acute myocardial infarction received either placebo (239 patients) or L-carnitine (233 patients) within 24 hours of onset of chest pain. The clinical end points—congestive heart failure and death after discharge—of 6 percent in the L-carnitine treatment group and 9.6 percent in the placebo group, predict enhanced survival of individuals given L-carnitine after an MI. [51]

Ghidini et al gave L-carnitine (1 g twice daily for 45 days) to 21 patients with congestive heart failure secondary to ischemic and/or hypertensive heart disease. Conventional therapy (digitalis, diuretics, antiarrhythmic agents) was also administered in all cases. They observed a distinct improvement in heart rate, serum cholesterol and triglyceride levels, edema and dyspnea, as well as increased diuresis, and a marked reduction in daily digitalis consumption in those given L-carnitine.[52]

HIV and Immunity

Experimental results suggest L-carnitine could be an effective anti-apoptotic drug, capable of increasing the absolute counts of CD4 and CD8 lymphocytes. Moretti et al conducted a preliminary investigation to ascertain the impact of long-term L-carnitine administration on CD4 and CD8 absolute counts, rate, and apoptosis in HIV-1-infected subjects. 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 four months. L-carnitine therapy resulted in an increase of absolute CD4 counts, which was statistically significant on days 90 and 150. A positive, though not significant trend was also observed in the change in absolute counts of CD8 lymphocytes.[53] Cifone et al have also found that administration of L-carnitine is capable of inducing a strong reduction in the percentage of both CD4 and CD8 cells undergoing apoptosis. Their work suggests L-carnitine might partially accomplish this reduction in apoptosis by decreasing peripheral blood mononuclear cell-associated ceramide, an intracellular messenger of apoptosis.[54]

Administration of L-carnitine (6 g/day for two weeks) to AIDS patients treated with zidovudine has been shown to result in increased PBMCs proliferation, as well as a reduction in serum levels of beta 2-microglobulin and circulating tumor necrosis factor (TNF)-alpha.[55]

Hypoglycemia

Since one of the manifestations of carnitine deficiency is hypoglycemia, it is not surprising that several investigators have reported a beneficial impact of L-carnitine administration on plasma glucose and insulin levels following intravenous infusion of glucose. Negro et al observed that the addition of both 2 g and 4 g of L-carnitine to 500 ml solutions of 5 percent and 10 percent glucose reduced the increase in plasma glucose levels.[56] Grandi et al reported a similar improvement in glucose metabolism following the addition of 2 g of L-carnitine to a 5-percent glucose solution.[57] Whether these observations would translate to a beneficial clinical effect in individuals with a tendency to reactive blood sugar is not currently known; however, due to the safety of L-carnitine and its tendency to improve fatigue (a common concomitant symptom of individuals with reactive blood sugar), a clinical trial with L-carnitine seems warranted.

Male Infertility

Increasingly, L-carnitine is being investigated as a potential therapeutic intervention in some forms of male infertility. It has been proposed that spermatozoa might require L-carnitine for maturation since a high concentration of L-carnitine is found in the epididymis. The spermatozoa, which require beta oxidation for energy, appear to concentrate L-carnitine.[58]

Oral administration of L-carnitine can improve sperm quality in some patients with idiopathic asthenospermia (defective sperm motility). Researchers provided 100 patients with 3 g daily of L-carnitine for four months and reported improvements in all assessed parameters of sperm motility, as well as an increase in the total sperm count.[59] Similar findings were reported in a similar group with asthenospermia. A favorable effect of 3 g/day of L-carnitine was noted on sperm motility, and rapid linear progression was seen in 37 out of 47 patients treated. Additionally, an average increase in the total number of sperm was demonstrated.[60]

Pregnancy and Pediatric Applications

Among the physiological changes characteristic of intrauterine development is an increase in body stores of carnitine, thought to occur due to the increased demand of the fetus on maternal supplies. Following delivery, interruption of the materno-fetal supply, along with the inability of the newborn to meet body requirements by endogenous synthesis, leaves the infant dependent upon exogenous intake. In circumstances of the absence of exogenous intake due to carnitine-free nutrition, tissue carnitine reserves decline in infants. Preterm infants are predictably in even greater jeopardy of having a relative carnitine deficiency.[61] In contrast, a gradual increase of carnitine stores is a normal response of infants to breast feeding or the use of carnitine-containing formulas.[62]

Genger et al have reported an increased need for carnitine during pregnancy. In a small trial of women with diagnosed placental insufficiency, they observed a tendency toward beneficial outcomes following carnitine administration (1 g twice daily orally for one week followed by 1 g daily for the second week). In spite of the small numbers in this trial, the relative short duration of supplementation combined with the trend toward improved outcomes certainly merits further investigation of L-carnitine for this condition.[63]

Since physiologically, L-carnitine activates surfactant synthesis, it is not surprising that supplementation to women with imminent premature delivery provides a substantial benefit to the infant in the postnatal period. Results indicate a combination of L-carnitine (4 g/day for five days) and betamethasone given to women in the prenatal period can reduce both the incidence of respiratory distress syndrome and the mortality of premature newborns. In this trial, the incidence of respiratory distress syndrome of infants was approximately one-half (7.3% vs 14.5%) and the mortality rate was 1.8 percent compared with 7.3 percent in the group receiving the combined intervention as compared to betamethasone alone.[64]

In a case of three siblings presenting with apnea and periodic breathing, along with biochemical defects consistent with a non-specific abnormality of beta oxidation, one of the infants died of sudden infant death syndrome; however, the two surviving infants had a rapid resolution of both respiratory and metabolic abnormalities subsequent to treatment with L-carnitine.[65]

Winter et al have suggested, based upon their clinical experience, that "secondary plasma carnitine deficiency is a common pediatric finding. The presence of failure to thrive, recurrent infections, hypotonia, encephalopathy, cardiomyopathy, or nonketotic hypoglycemia requires investigation of carnitine status."[66] These authors reported normalization of cardiomyopathy in eight infants subsequent to the correction of a secondary L-carnitine deficiency. Kothari and Sharma have also reported a modest improvement in left

ventricular function subsequent to administration of L-carnitine (50 mg/kg/day) in 13 children with idiopathic dilated cardiomyopathy.[67]

Progressive cardiomyopathy, with or without chronic muscle weakness, is the most common presentation (median age of onset, three years) in children with a defect in intracellular uptake of carnitine resulting in carnitine deficiency. Episodes of fasting hypoglycemia during the first two years of life are also a common presentation in affected infants. These children have low levels of plasma carnitine and a decreased rate of carnitine uptake. Typically, parents of affected children have intermediate values lying between those of normal control subjects and the affected children, suggestive of recessive inheritance. Stanley et al have suggested that early recognition of this disorder and the subsequent treatment with high doses of oral carnitine might be a life-saving intervention for these children.[68]

Carnitine deficiency might be a complicating factor in cystic fibrosis. Wos et al reported five cases of infants with cystic fibrosis, impaired liver function, and neurological symptoms who, subsequent to a high carnitine diet and enteral administration, experienced a concomitant improvement in clinical condition with the progressive normalization of serum carnitine levels.[69]

Rett Syndrome

Two case reports in the medical literature indicate administration of L-carnitine might provide some benefits to individuals with Rett syndrome. Plioplys and Kasnicka treated a 17-year-old female with L-carnitine (50 mg/kg/day). Over the two-month course of treatment an improvement in alertness, eye contact, and interaction with her environment were observed. These improvements were all lost following discontinuation of L-carnitine, and were regained after L-carnitine was reintroduced.[70]

Researchers administered L-carnitine (beginning at 75 mg/kg/day and increasing to 150 mg/kg/day) to a 3 1/2-year-old girl diagnosed with Rett syndrome. They observed improvements in physical activity, muscle hypotonia, communication, and sleep time. Similar to the findings of Plioplys and Kasnicka, a wash-out period followed by reintroduction of L-carnitine supplementation confirmed the efficacy of this regime.[71]

Precautions

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. However, since L-carnitine has been given to pregnant women late in pregnancy with resulting positive outcomes and since L-carnitine is a normally occurring component of the diet, it is unlikely this supplement has any negative impact on pregnancy in normally supplemented amounts. In general, the recommendation for its use follows that of other nutritional substances which have not been overtly studied during human pregnancy; that being, use the supplement cautiously and only if clearly indicated by either laboratory or clinical status.

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.

Adverse Reactions

A variety of mild gastrointestinal symptoms have been reported, including transient nausea and vomiting, abdominal cramps, and diarrhea. A change in body odor has also been observed in a few individuals. Typically, reducing the dose will result in improvements in these adverse reactions.

No reports of L-carnitine toxicity from overdosage exist. In mice, the LD50 is 19.2 g/kg. Studies indicate no mutagenicity; however, experiments to determine the long-term carcinogenicity have not been conducted.

Dosage

As a general guideline, the average therapeutic dose is 1000 mg given two to three times daily for a total of 2000-3000 mg. No advantage appears to exist in giving an oral dose greater than 2000 mg at one time, since absorption studies indicate saturation at this dose.

Conclusions

L-carnitine has been used as a nutritional supplement for more than two decades. Although it has a well-deserved reputation as a safe and effective addition to nutritional protocols for a range of clinical conditions, its therapeutic role in coronary disease is perhaps its primary claim to fame. Addition of L-carnitine to a protocol for angina and ischemia results in improved exercise tolerance, reduced frequency of angina episodes, and beneficial changes to the ECG. L-carnitine seems to predictably improve risk factor markers of coronary disease; however, the single most impressive aspect of L-carnitine supplementation in coronary conditions has been the consistent bottom-line impact in reducing the clinical end point of congestive heart failure mortality. With additional research now indicating a place for L-carnitine in assisting with clinically challenging conditions such as chronic fatigue syndrome, HIV, and hypoglycemia, and with the ever expanding role of L-carnitine in pediatric health, it appears the use of this dietary supplement will continue to expand.

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