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Role of L-Carnitine Therapy in Different Clinical Indications

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Abstract: *L-carnitine (Levocarnitine) was originally discovered in 1905 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.*

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. With additional research now indicating a place for L-carnitine in assisting with clinically challenging conditions such as dyslipidemia, Anorexia, Athletic performance, male infertility, Renal failure, diabetes, 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.

L-carnitine is indicated in the treatment of primary systemic carnitine deficiency. L-carnitine can be used in acute and chronic treatment of patients with an inborn error of metabolism which results in a secondary carnitine deficiency.

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.[1,2]

L-carnitine has been used as a nutritional supplement for more than two decades. 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.[1,2]

Mechanism of Action

Carnitine primary mechanism of action is apparently attributable to its role as a cofactor in the transformation of free long-chain fatty acids into acyl-carnitines for subsequent transport into the mitochondrial matrix. Carnitine is involved in the metabolism of ketones for energy and the conversion of branched-chain amino acids – valine, leucine, and isoleucine – into energy.[1]

Dietary Intake and Synthesis

Recent findings on the biosynthesis of L-Carnitine in mammals have been reviewed recently. The main dietary sources of L-Carnitine are meats, particularly red meats, and dairy products, whereas fruit and vegetables contain negligible quantities of the compound. Although the endogenous levels of L-Carnitine can be affected by long-term changes in the level of dietary intake and nutritional status, under normal conditions healthy humans can

synthesize sufficient amounts of the compound, which is why it is not regarded as a true vitamin.[3]

L-Carnitine 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.[4,5]

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. 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.[6]

Clinical Uses

Heart Disease (General)

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. 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.[7]

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.[3]

Cardiogenic Shock

Corbucci and Lettieri et al, 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.[4] In a follow-up study, a similar positive trend was noted in terms of survival rate in individuals administered L-carnitine for cardiogenic shock.[8]

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.[9]

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-yearold 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 20-10 mm.[10]

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 ischemic 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 angina 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%).[11]

Dyslipidemia

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. L-Carnitine supplementation (2 g daily) also decreased triglycerides in individuals with essential hypertension. 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. [12]

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. 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.[12]

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.[13] 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.[13]

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 antihistamine 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.[14]

Athletic Performance

Supplementation with L-carnitine induced a significant post-exercise decrease of plasma lactate and pyruvate and a concurrent increase of acetylcarnitine. 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.[12]

While some of the results with L-carnitine supplementation have been promising, not all research is in agreement. Heinonen et al, 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.[24] 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.[12]

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.[15]

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.

HIV and Immunity

Experimental results suggest Lcarnitine 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. 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.[16]

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. 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.[11]

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. 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. 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.[17]

Pregnancy and Pediatric Applications

Preterm infants are predictably in even greater jeopardy of having a relative carnitine deficiency. In contrast, a gradual increase of carnitine stores is a normal response of infants to breast feeding or the use of carnitine-containing formulas. Genger et al have reported an increased need for carnitine during pregnancy. 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.[16]

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.[16]

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. 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.[18]

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. [18]

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.[19]

Conclusions:

L-carnitine is indicated in the treatment of primary systemic carnitine deficiency. L-carnitine can be used in acute and chronic treatment of patients with an inborn error of metabolism which results in a secondary carnitine deficiency. Carnitine supplementation may enhance insulin resistance, inflammatory and antioxidant status, protein balance, lipid profile, and cardiac function. Carnitine administration can be useful for selected patients on dialysis, male infertility patients who do not adequately respond to standard therapy.

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