L-carnitine

L-carnitine is a derivative of the amino acid, lysine. Its name is derived from the fact that it was first isolated from meat (*carnus*) in 1905. Only the L-isomer of carnitine (Figure 1) is biologically active. L-carnitine appeared to act as a vitamin in the mealworm (*Tenebrio molitor*), and was therefore termed vitamin B_T. Vitamin B_T, however, is actually a misnomer because humans and other higher organisms can synthesize L-carnitine. Under certain conditions, the demand for L-carnitine may exceed an individual's capacity to synthesize it, making it a conditionally essential micronutrient.

Metabolism and Bioavailability

In healthy people, carnitine homeostasis (balance) is maintained through endogenous biosynthesis of L-carnitine, absorption of carnitine from dietary sources, and elimination and reabsorption of carnitine by the kidneys.

Endogenous Biosynthesis

Humans can synthsize L-carnitine from the amino acids lysine and methionine in a multi-step process. Specifically, protein-bound lysine is enzymatically methylated to form episilon-N-trimethyllysine; three molecules of methionine provide the methyl groups for the reaction. Epsilon-N-trimethyllysine is released for carnitine synthesis through normal mechanisms of protein hydrolysis. Several enzymes are involved in endogenous L-carnitine biosynthesis. The enzyme gamma-butyrobetaine hydroxylase, however, is absent from cardiac and skeletal muscle but highly expressed in human liver, testes, and kidney. The rate of L-carnitine biosynthesis in humans was studied in vegetarians and is estimated to be 1.2 micromol/kg of body weight/day. Changes in dietary carnitine intake or renal reabsorption do not appear to effect the rate of endogenous carnitine synthesis.

Absorption of Exogenous L-Carnitine

Dietary L-Carnitine

L-carnitine is absorbed from foods via both active and passive transport across enterocyte (intestinal cell) membranes. The bioavailability of L-carnitine can vary depending on dietary composition. For instance, one study reports that bioavailability of L-carnitine in individuals adapted to low-carnitine diets (i.e., vegetarians) is higher than those adapted to high-carnitine diets (i.e., regular red meat eaters; 66%-86% versus 54%-72%).

L-Carnitine Supplements

While bioavailability of L-carnitine from the diet is quite high, absorption from oral L-carnitine supplements is considerably lower. Supplemental L-carnitine is mainly absorbed by passive diffusion. According to one study, bioavailability of L-carnitine from oral supplements (0.5-6 gram dosage) ranges from 14%-18% of the total dose. Less is known regarding the metabolism of the acetylated form of L-carnitine, acetyl-L-carnitine (ALCAR); however, bioavailability of ALCAR is thought to be higher than L-carnitine. The results of *in vitro* experiments suggest that ALCAR is partially hydrolyzed upon intestinal absorption. In humans, administration of 2 grams of ALCAR per day for 50 days increased plasma ALCAR levels by 43%, suggesting that some acetyl-L-carnitine is absorbed without hydrolysis or that L-carnitine is reacetylated in the enterocyte.

Elimination and Reabsorption

L-carnitine and short-chain acylcarnitines (esters of L-carnitine), such as acetyl-L-carnitine, are excreted by the kidneys. Renal reabsorption of L-carnitine is normally very efficient; in fact, an estimated 95% is thought to be reabsorbed by the kidneys. Therefore, carnitine excretion by the kidney is normally very low. However, several conditions can decrease carnitine reabsorption efficiency and, correspondingly, increase carnitine excretion. Such conditions include high-fat (low-carbohydrate) diets, high-protein diets, pregnancy, and certain disease states. In addition, when circulating L-carnitine levels increase, as in the case for oral supplementation, renal reabsorption of L-carnitine becomes saturated, resulting in increased urinary

excretion of L-carnitine. Dietary or supplemental L-carnitine that is not absorbed by enterocytes is degraded by colonic bacteria to form two principal products, trimethylamine and gamma-butyrobetaine. Gamma-butyrobetaine is eliminated in the feces; trimethylamine is efficiently absorbed and metabolized to trimethylamine-N-oxide, which is excreted in the urine.

Biological Activity

Mitochondrial Oxidation of Long-Chain Fatty Acids

L-carnitine is synthesized primarily in the liver but also in the kidneys, and then it must be transported to other tissues. It is most concentrated in tissues that use fatty acids as their primary dietary fuel, such as skeletal and cardiac (heart) muscle. In this regard, L-carnitine plays an important role in energy production by chaperoning activated fatty acids (acyl-CoA) into the mitochondrial matrix for metabolism and chaperoning intermediate compounds out of the mitochondrial matrix to prevent their accumulation.

L-carnitine is required for mitochondrial beta-oxidation of long-chain fatty acids for energy production. Long-chain fatty acids must be in the form of esters of L-carnitine (acylcarnitines) in order to enter the mitochondrial matrix where beta-oxidation occurs. Proteins of the carnitine-acyl transferase family transport acylcarnitines into the mitochondrial matrix. On the outer mitochondrial membrane, carnitine-palmitoyl transferase I (CPTI) catalyzes the transfer of long-chain fatty acids into the cytosol from coenzymeA (CoA) to L-carnitine, the rate limiting step in fatty acid oxidation. A transporter protein called carnitine:acylcarnitine translocase (CACT) facilitates the transport of acylcarnitine esters across the inner mitochondrial membrane. On the inner mitochondrial membrane, carnitine-palmitoyl transferase II (CPTII) catalyzes the transfer of fatty acids from L-carnitine to free CoA in the mitochondrial matrix, where they are metabolized through beta-oxidation, ultimately yielding propionyl-CoA and acetyl-CoA.

Regulation of Energy Metabolism through Modulation of Acyl CoA:CoA Ratio

CoA is required as a cofactor for numerous cellular reactions. Within the mitochondrial matrix, carnitine acetyl transferase (CAT) catalyzes the trans-esterification (transfer) of short- and medium-chain fatty acids from CoA to carnitine. The acylcarnitine esters can then be exported from the mitochondria via CACT, and the resulting free CoA can participate in other reactions. For example, pyruvate dehydrogenase (PDH) catalyzes the formation of acetyl CoA from pyruvate and free CoA. Acetyl CoA, in turn, can be oxidized to produce energy (ATP) in the tricarboxylic acid (TCA) cycle. Carnitine facilitates the oxidation of glucose by removing acyl groups generated by fatty acid beta-oxidation and freeing CoA to participate in the PDH reaction.

Deficiency

Nutritional carnitine deficiencies have not been identified in healthy people without metabolic disorders, suggesting that most people can synthesize enough L-carnitine. Even strict vegetarians (vegans) show no signs of carnitine deficiency, despite the fact that most dietary carnitine is derived from animal sources. Infants, particularly premature infants, are born with low stores of L-carnitine, which could put them at risk of deficiency given their rapid rate of growth. One study reports that infants fed carnitine-free, soy-based formulas grew normally and showed no signs of a clinically relevant carnitine deficiency; however, some biochemical measures related to lipid metabolism differed significantly from infants fed the same formula supplemented with L-carnitine. Soy-based infant formulas are now fortified with the amount of L-carnitine normally found in human milk.

Primary Systemic Carnitine Deficiency

Primary systemic carnitine deficiency is a rare, autosomal recessive disorder caused by mutations in the carnitine transporter protein OCTN2. Afflicted individuals have poor intestinal absorption of dietary L-carnitine and impaired L-carnitine reabsorption by the kidneys, i.e., increased urinary loss of L-carnitine. The disorder usually presents in early childhood, and is characterized by low plasma carnitine, progressive cardiomyopathy, skeletal myopathy, hypoglycemia and hypoammonemia. Without treatment, primary systemic carnitine deficiency is fatal. Treatment consists of pharmacological doses of L-carnitine; such therapy corrects the cardiomyopathy and muscle weakness.

Myopathic Carnitine Deficiency

Primary myopathic carnitine deficiency is a rare, genetic disorder in which the carnitine deficiency is limited to skeletal and cardiac muscle. Symptoms, including muscle pain and progressive muscle weakness, begin in childhood or adolescence. Serum carnitine levels, however, are usually normal. In general, the myopathic form of primary carnitine deficiency is less severe than the systemic form.

Secondary Carnitine Deficiency or Depletion

Secondary carnitine deficiency or depletion may result from either genetic or acquired conditions. Hereditary causes include genetic defects in amino acid degradation (e.g., propionic aciduria) and lipid metabolism (e.g., medium chain acyl-CoA dehydrogenase deficiency). Such inherited disorders can lead to a build-up of organic acids, which are subsequently removed from the body via urinary excretion of acylcarnitine esters. Increased urinary losses of carnitine can lead to a systemic depletion of carnitine. Systemic carnitine depletion can also occur in disorders of impaired renal reabsorption. For instance, Fanconi's syndrome is a hereditary or acquired condition in which the kidney's proximal tubular reabsorption function is impaired. Malfunction of the kidney consequently results in increased urinary

losses of carnitine. One example of an exclusively acquired carnitine deficiency involves chronic use of pivalate-conjugated antibiotics. Pivalate is a branched-chain fatty acid that is metabolized to form an acylCoA ester that is transesterified to carnitine and subsequently excreted in the urine as pivaloyl carnitine. Urinary losses of carnitine via this route can be 10-fold greater than the sum of daily carnitine intake and biosynthesis; thus, systemic carnitine depletion can result. Further, patients with renal disease who undergo hemodialysis are at risk for secondary carnitine deficiency because hemodialysis removes carnitine from the blood. Regardless of etiology, a secondary carnitine deficiency is characterized clinically by low plasma concentrations of free carnitine (less than 20 micromol/L) and increased acylcarnitine/free carnitine ratios (greater than 0.4). Secondary deficiencies are more common than the rare, primary carnitine disorders.

Nutrient Interactions

Endogenous biosynthesis of L-carnitine is catalyzed by the concerted action of five different enzymes. This process requires two essential amino acids (lysine and methionine), iron (Fe^{2+}), vitamin C, vitamin B_6, and niacin in the form of nicotinamide adenine dinucleotide (NAD). One of the earliest symptoms of vitamin C deficiency is fatigue, thought to be related to decreased synthesis of L-carnitine.

Disease Prevention

Aging

Age-related declines in mitochondrial function and increases in mitochondrial oxidant production are thought to be important contributors to the adverse effects of aging. Tissue L-carnitine levels have been found to decline with age in humans and animals. One study found that feeding aged rats acetyl-L-carnitine (ALCAR) reversed the age-related declines in tissue L-carnitine levels and also reversed a number of age-related changes in liver mitochondrial

function; however, high doses of ALCAR increased liver mitochondrial oxidant production. More recently, two studies found that supplementing aged rats with either ALCAR or alpha-lipoic acid, a mitochondrial cofactor and antioxidant, improved mitochondrial energy metabolism, decreased oxidative stress, and improved memory. Interestingly, co-supplementation of ALCAR and alpha-lipoic acid resulted in even greater improvements than either compound administered alone. Likewise, several studies have reported that supplementing rats with both L-carnitine and alpha-lipoic acid blunts the age-related increases in reactive oxygen species (ROS), lipid peroxidation, protein carbonylation, and DNA strand breaks in a variety of tissues (heart, skeletal muscle, brain). Improvements in mitochondrial enzyme and respiratory chain activities were also observed. While these findings are very exciting, it is important to realize that these studies used relatively high doses (100 to 300 mg/kg body weight/day) of the compounds and only for a short time (one month). It is not yet known whether taking relatively high doses of these two naturally occurring substances will benefit rats in the long-term or will have similar effects in humans. Clinical trials in humans are planned, but it will be several years before the results are available.

Disease Treatment

Cardiovascular Disease

In the studies discussed below it is important to note that treatment with L-carnitine or propionyl-L-carnitine was used as an adjunct (in addition) to appropriate medical therapy not in place of it.

Myocardial Infarction (Heart Attack)

Myocardial infarction (MI) occurs when an atherosclerotic plaque in a coronary artery ruptures. The resultant clot can obstruct the blood supply to the heart muscle, causing injury or damage to the heart. L-carnitine treatment has been found to reduce injury to heart muscle resulting from ischemia in several animal models. In humans, L-

carnitine administration immediately after MI diagnosis has improved clinical outcomes in several, small clinical trials. In one trial, half of 160 men and women diagnosed with a recent MI were randomly assigned to receive 4 grams/day of L-carnitine in addition to standard pharmacological treatment. After one year of treatment, mortality was significantly lower in the L-carnitine supplemented group compared to the control group (1.2% vs. 12.5%), and angina attacks were less frequent. However, not all clinical trials have found L-carnitine supplementation to be beneficial after MI. In a randomized, double-blind, placebo-controlled trial, 60 men and women diagnosed with an acute MI were treated with either intravenous L-carnitine (6 grams/day) for seven days followed by oral L-carnitine (3 grams/day) for three months or placebo. After three months, mortality did not differ between the two groups, nor did echocardiographic measures of cardiac function. In a larger placebo-controlled trial, 472 patients treated in an intensive care unit within 24 hours of having their first MI were randomly assigned to either intravenous L-carnitine therapy (9 grams/day) for five days followed by oral L-carnitine (6 grams/day) for 12 months or a placebo; both groups also received standard medical therapy. Although there were no significant differences in mortality or the incidence of congestive heart failure (CHF), left ventricular volumes were significantly lower in the L-carnitine treated group at the end of one year, suggesting that L-carnitine therapy may limit adverse effects of acute MI on the heart muscle. Based on these findings, a randomized placebo-controlled trial in 2,330 patients with acute MI was undertaken to determine the effect of L-carnitine therapy on the incidence of heart failure six months after MI. L-carnitine therapy did not affect the incidence of heart failure and death in this study.

Heart Failure

Heart failure is described as the heart's inability to pump enough blood for all of the body's needs. In coronary artery disease, accumulation of atherosclerotic plaque in the coronary arteries may prevent heart regions from getting adequate circulation, ultimately

resulting in cardiac damage and impaired pumping ability. Myocardial infarction (MI) may also damage the heart muscle, which could potentially lead to heart failure. Because physical exercise increases the demand on the weakened heart, measures of exercise tolerance are frequently used to monitor the severity of heart failure. Echocardiography is also used to determine the left ventricular ejection fraction (LVEF), an objective measure of the heart's pumping ability. A LVEF of less than 40% is indicative of systolic heart failure.

Addition of L-carnitine to standard medical therapy for heart failure has been evaluated in several clinical trials. A randomized, placebo-controlled study in 70 heart failure patients found that three-year survival was significantly higher in the group receiving L-carnitine (2 grams/day) compared to the group receiving placebo. In a randomized, single-blind, placebo-controlled trial in 30 heart failure patients, oral administration of 1.5 grams/day of propionyl-L-carnitine for one month resulted in significantly improved measures of exercise tolerance and a slight but significant decrease in left ventricular size, in comparison to placebo. A larger randomized, double-blind, placebo-controlled trial compared the addition of propionyl-L-carnitine (1.5 grams/day for six months) to the treatment regimen of 271 heart failure patients to a placebo group consisting of 266 patients. Overall, exercise tolerance was not different between the two groups. However, in patients with higher LVEF values (greater than 30%), exercise tolerance was significantly improved in the propionyl-L-carnitine versus placebo group, suggesting that propionyl-L-carnitine may help improve exercise tolerance in higher functioning heart failure patients.

Angina Pectoris

Angina pectoris is chest pain that occurs when the coronary blood supply is insufficient to meet the metabolic needs of the heart muscle (ischemia). The addition of L-carnitine or propionyl-L-carnitine to pharmacologic therapy for chronic stable angina has been found to

modestly improve exercise tolerance and decrease electrocardiographic signs of ischemia during exercise testing in a limited number of angina patients. One randomized, placebo-controlled study in 200 patients with exercise-induced stable angina found that supplementing conventional medical therapy with 2 grams/day of L-carnitine for six months significantly reduced the incidence of premature ventricular contractions at rest and also improved exercise tolerance. In addition, a randomized, placebo-controlled cross-over trial in 44 men with chronic stable angina found that administering 2 grams/day of L-carnitine for four weeks significantly increased the exercise workload tolerated prior to the onset of angina and decreased ST segment depression (electrocardiographic evidence of ischemia) during exercise compared to placebo. In a more recent randomized, placebo-controlled trial in 47 men and women with chronic stable angina, the addition of 2 grams/day of L-carnitine for three months significantly improved exercise duration and decreased the time required for exercise-induced ST segment changes to return to baseline, in comparison to placebo. One study examined the effect of propionyl-L-carnitine on ischemia in men with myocardial dysfunction and angina pectoris by measuring hemodynamic and angiographic variables before, during, and after administering propionyl-L-carnitine (15 mg/kg body weight). In this study, propionyl-L-carnitine decreased myocardial ischemia, evidenced by significant reductions in ST-segment depression and left ventricular end-diastolic pressure. Although these results are promising, large-scale studies are needed to determine whether L-carnitine or propionyl-L-carnitine is a beneficial therapy for angina pectoris.

Intermittent Claudication in Peripheral Arterial Disease

In peripheral arterial disease, atherosclerosis of the arteries that supply the lower extremities may diminish blood flow to the point that the metabolic needs of exercising muscles are not sufficiently met, thereby leading to ischemic leg or hip pain known as claudication. In a randomized, placebo-controlled study of 495

patients with intermittent claudication, 2 grams/day of propionyl-L-carnitine for 12 months significantly increased maximal walking distance and the distance walked prior to the onset of claudication in patients whose initial maximal walking distance was less than 250 meters. However, no significant response to propionyl-L-carnitine treatment was observed in more mildly affected patients whose initial maximal walking distance was greater than 250 meters. In a double-blind, randomized, placebo-controlled trial of 155 patients with disabling claudication in the U.S. and Russia, administration of 2 grams/day of propionyl-L-carnitine for six months significantly improved walking distance and claudication onset time compared to placebo. One study compared the efficacy of L-carnitine and propionyl-L-carnitine administered intravenously for the treatment of intermittent claudication and concluded that propionyl-L-carnitine was more effective than L-carnitine when the same amount of carnitine was provided. Moreover, propionyl-L-carnitine has been reported to be a vasodilator; thus, the results mentioned above may in part be due to this compound's ability to effect endothelial function. In fact, a recent double-blind, placebo-controlled, cross-over study in 21 peripheral arterial disease patients found that intravenous infustion of propionyl-L-carnitine (6 grams/day) increased flow-mediated dilation of the brachial artery.

End-State Renal Failure/Hemodialysis

L-carnitine and many of its precursors are removed from the circulation during hemodialysis. Impaired L-carnitine synthesis by the kidneys may also contribute to the potential for carnitine deficiency in patients with end-stage renal failure undergoing hemodialysis. The U.S. Food and Drug Administration (FDA) has approved the use of L-carnitine in hemodialysis patients for the prevention and treatment of carnitine deficiency. Carnitine depletion may lead to a number of conditions observed in dialysis patients, including muscle weakness and fatigue, plasma lipid abnormalities, and refractory anemia. A systematic review that examined the results of 18 randomized trials, including a total of 482 dialysis patients, found that L-carnitine

treatment improved hemoglobin levels in studies performed before recombinant erythropoietin (EPO) was routinely used to treat anemia in dialysis patients, and that L-carnitine treatment decreased EPO dose and resistance to EPO in studies performed when patients routinely received EPO. Although some uncontrolled studies found that L-carnitine treatment improved blood lipid profiles in hemodialysis patients, the cited systematic review of randomized controlled trials found no evidence that L-carnitine improved lipid profiles. The National Kidney Foundation (NKF) does not recommend routine administration of L-carnitine to all dialysis patients. However, the NKF and other consensus groups suggest a trial of L-carnitine for hemodialysis patients with selected symptoms that do not respond to standard therapy. Those symptoms include persistent muscle cramps or hypotension (low blood pressure) during dialysis, severe fatigue, skeletal muscle weakness or myopathy, cardiomyopathy, and anemia requiring large doses of EPO. In general, intravenous L-carnitine therapy (20 mg/kg body weight) at the end of a dialysis session has been recommended for patients on hemodialysis. Oral carnitine is not advised for hemodialysis patients due to the possible accumulation of potentially toxic metabolites.

Alzheimer's Disease (Dementia)

Several small, controlled clinical trials conducted in the 1990's suggested that acetyl-L-carnitine (ALCAR) treatment (2-3 grams/day for 6-12 months) might slow the cognitive decline in patients clinically diagnosed with Alzheimer's disease. However, a larger multicenter, randomized controlled trial involving 417 Alzheimer's disease patients found ALCAR treatment (3 grams/day for 12 months) was no different than placebo with respect to cognitive decline. Subsequent statistical analyses of the data from that study suggested that patients with early-onset Alzheimer's disease (65 years and younger) experienced a more rapid cognitive decline that was significantly slowed by ALCAR treatment. However, a multicenter, randomized controlled trial involving 167 early-onset Alzheimer's disease patients between 45 and 65 years of age found that ALCAR

treatment (3 grams/day for 12 months) had no effect on most measures of cognitive decline except ALCAR treatment was associated with a non-significant reduction in the attention-related decline compared to placebo.

HIV/AIDS

One of the hallmarks of infection with the HIV retrovirus is a progressive decline in the numbers of critical immune cells known as CD4 T lymphocytes (CD4 cells), ultimately leading to the development of AIDS. Lymphocytes of HIV-infected individuals inappropriately undergo programmed cell death (apoptosis). Limited evidence in cell culture experiments and in humans suggests that L-carnitine supplementation may help slow or prevent HIV-induced lymphocyte apoptosis. In an uncontrolled trial, 11 asymptomatic HIV-infected patients, who had refused antiretroviral treatment despite progressively declining CD4 cell counts, were treated with 6 grams/day of L-carnitine intravenously for four months. After four months of L-carnitine therapy, CD4 cell counts increased significantly and markers of lymphocyte apoptosis decreased, although there was no significant change in plasma levels of the HIV virus. Long-term outcomes were not reported in these patients.
In a more recent study, 20 HIV-infected individuals were randomly assigned to receive the antiretroviral agents, zidovudine (AZT) and didanosine (DDI), with or without supplemental L-carnitine. Although CD4 cell counts and plasma HIV levels were not different between the two groups after seven months of therapy, indicators of CD4 cell apoptosis were significantly lower in the group taking L-carnitine.

Some antiretroviral agents (nucleoside analogues) used to treat HIV-infection appear to cause a secondary L-carnitine deficiency that may lead to some of their toxic side effects (see Drug Interactions). A small cross-sectional study found that nerve concentrations of acetyl-L-carnitine were significantly lower in HIV patients who developed peripheral neuropathy while taking nucleoside analogues than in

control subjects. Ten out of 16 HIV patients with painful neuropathies reported improvement after three weeks of intravenous or intramuscular acetyl-L-carnitine (ALCAR) treatment. In a small study of 20 patients with antiretroviral-induced neuropathy, oral ALCAR (2 grams/day) for four weeks mean pain intensity score but did not affect any of the measured neurophysiological parameters. Results from two recent trials suggest that long-term (two to four years) ALCAR supplementation may be a beneficial adjunct to antiretroviral therapy in some HIV-infected individuals. However, large-scale, controlled studies are needed before any conclusions can be drawn.

Decreased Sperm Motility

L-carnitine is concentrated in the epididymis, where sperm mature and acquire their motility. Two uncontrolled trials of L-carnitine supplementation in more than 100 men diagnosed with decreased sperm motility found that oral L-carnitine supplementation (3 grams/day) for three to four months significantly improved sperm motility. However, no information on subsequent fertility was reported. A cross-sectional study of 101 fertile and infertile men found that L-carnitine concentrations in semen were positively correlated with the number of sperm, the percentage of motile sperm, and the percentage of normal appearing sperm in the sample, suggesting that L-carnitine levels in semen may be useful in evaluating male infertility. More recently, a placebo-controlled, double-blind, cross-over trial in 86 patients with male infertility found that L-carnitine (2 grams/day) supplementation for two months led to significantly improvements in sperm quality, evidenced by increases in sperm concentration and motility. Similar improvements in sperm motility were observed in a subsequent placebo-controlled, double-blind, randomized study conducted by the same group, but the patients received combination therapy consisting of L-carnitine (2 grams/day) and acetyl-L-carnitine (1 gram/day) for six months. Interestingly, in both studies, the most dramatic carnitine-induced improvements were noted in patients with the lowest baseline sperm

motility measures (i.e., most severe cases). Another group of researchers also reported improved sperm motility following combined carnitine therapy. In this placebo-controlled, double-blind, randomized study, 44 patients with idiopathic asthenozoospermia (reduced sperm motility) received placebo, L-carnitine (3 grams/day), acetyl-L-carnitine (3 grams/day), or a combination of L-carnitine (2 grams/day) and acetyl-L-carnitine (1 gram/day). The combination therapy as well as acetyl-L-carnitine, alone, resulted in significant increases in sperm motility. Together, these data suggest that carnitine therapy may be useful in disorders of sperm motility and male infertility; however, large-scale clinical trials are undoubtedly necessary.

Physical Performance

Interest in the potential of L-carnitine supplementation to improve athletic performance is related to its important roles in energy metabolism. A number of small, uncontrolled studies have reported that either acute (dose given one hour before exercise bout) or short-term (two to three weeks) L-carnitine supplementation (2 to 4 grams/day) was associated with increases in maximal oxygen uptake and decreases in plasma lactate. Most studies to date have shown no effect of L-carnitine supplementation on physical performance. However, conclusions that can be drawn from this research are limited due to small numbers of participants, short duration of supplementation, and lack of appropriate control groups in most studies. Several studies have shown that carnitine supplementation increases plasma carnitine levels, but studies have failed to demonstrate that carnitine supplementation increases levels of carnitine within skeletal muscle, the site of greater than 95% of the body's total carnitine. Thus, while carnitine supplementation in theory might work, the available data suggest that carnitine supplementation does not affect athletic performance in healthy individuals.

Sources of L-carnitine

Biosynthesis

The normal rate of L-carnitine biosynthesis in humans ranges from 0.16 to 0.48 mg/kg of body weight/day. Thus, a 70 kg (154 1b) person would synthesize between 11 and 34 mg of carnitine per day. This rate of synthesis combined with efficient (95%) L-carnitine reabsorption by the kidneys is sufficient to prevent deficiency in generally healthy people, including strict vegetarians.

Food Sources

Meat, poultry, fish, and dairy products are the richest sources of L-carnitine, while fruits, vegetables, and grains contain relatively little L-carnitine. Omnivorous diets have been found to provide 20 to 200 mg/day of L-carnitine for a 70 kg person, while strict vegetarian diets may provide as little as 1 mg/day for a 70 kg person. Between 63% and 75% of L-carnitine from food is absorbed, compared to 14%-20% from oral supplements. Non-milk based infant formulas (e.g., soy formulas) should be fortified so that they contain 11 mg of L-carnitine/liter. Some carnitine-rich foods and their carnitine content in milligrams (mg) are listed in the table below.

L-Carnitine Content of Selected Foods		
Food	**Serving**	**L-Carnitine (mg)**
Beef steak	3 ounces*	81
Ground beef	3 ounces	80
Pork	3 ounces	24
Canadian bacon	3 ounces	20
Milk (whole)	8 fluid ounces (1 cup)	8
Fish (cod)	3 ounces	5
Chicken breast	3 ounces	3
Ice cream	4 ounces (1/2 cup)	3
Avocado	1 medium	2
American cheese	1 ounce	1
Whole-wheat bread	2 slices	0.2

Asparagus	6 spears (1/2 cup)	0.2

*A 3-ounce serving of meat is about the size of a deck of cards.

Supplements

Intravenous L-carnitine is available only for the treatment of primary and secondary L-carnitine deficiencies.

Oral L-carnitine is available for the treatment of primary and secondary L-carnitine deficiencies. It is also available as a nutritional supplement; supplemental doses usually range from 500 mg to 2,000 mg/day.

Acetyl-L-carnitine is available without a prescription as a nutritional supplement. In addition to providing L-carnitine, it provides acetyl groups, which may be used in the formation of the neurotransmitter, acetylcholine. Supplemental doses usually range from 500 mg to 2,000 mg/day.

Propionyl-L-carnitine is available in Europe but not the U.S. It provides L-carnitine as well as propionate, which may be utilized as an intermediate during energy metabolism.

Safety

Adverse Effects

In general, L-carnitine appears to be well tolerated; toxic effects related to L-carnitine overdose have not been reported. L-carnitine supplementation may cause mild gastrointestinal symptoms, including nausea, vomiting, abdominal cramps and diarrhea. Supplements providing more than 3,000 mg/day may cause a "fishy" body odor. Acetyl-L-carnitine has been reported to increase agitation in some Alzheimer's disease patients and to increase seizure frequency and/or severity in some individuals with seizure disorders (95). Only the L-isomer of carnitine is biologically active, and the D-isomer may

actually compete with L-carnitine for absorption and transport, thereby increasing the risk of L-carnitine deficiency. Supplements containing a mixture of the D- and L-isomers (D,L-carnitine) have been associated with muscle weakness in patients with kidney disease. Controlled studies examining the safety of L-carnitine supplementation in pregnant and breastfeeding women are lacking.

Drug Effects

The anticonvulsant, valproic acid, and nucleoside analogues used in the treatment of HIV infection, including zidovudine (AZT), didanosine (ddI), zalcitabine (ddC) and stavudine (d4T), may produce a secondary L-carnitine deficiency. Pivalic acid-containing antibiotics used in Europe (pivampicillin, pivmecillinam and pivcephalexin) may also produce a secondary L-carnitine deficiency. Additionally, two cancer chemotherapy agents, ifosfamide and cisplatin, may increase the risk of secondary L-carnitine deficiency. Further, there is limited evidence that L-carnitine supplementation may help prevent cardiomyopathy induced by doxorubicin (adriamycin) therapy.