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Carnitine, metabolism and its pharmacokinetic significance

Eizadi Mojtaba*, Khorshidi Davood, Seyedhoseini MohammadAli, Dooaly Hussein

Department of Physical Education and Sport Science, Central Tehran Branch, Islamic Azad University, Iran

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Abstract

Carnitine is an essential nitrogenous nutrition that is facilitates transport of branched-chain fatty acid into mitochondria. This substrate has to potential role in energy production during fetus, newborn and adult years. The carnitine vital role is important in improving of some diseases such as diabetic, hemodyalis, HIV, carnitine genetic deficiency, man infertility, weight loss and exercise functional. The drug use and exercise supplemental from carnitine led not to strenuous accidents in disease and sport. The diagnosis of benefit effects of carnitine need to numerous study.

*Corresponding Author: Eizadi Mojtaba ✉ izadimojtaba2006@yahoo.com

Carnitine Chemical structure and Sources

Carnitine (3-carboxy-2-hydroxy-propyl tri-methyl ammonium hydroxide) is a nitrogen compound that occurs naturally in skeletal muscle, heart, kidney, plasma and other tissues are capable of fatty acid oxidation and its fundamental role is in the transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix (Harper *et al.,* 1998). It isometric forms are L-Carnitine and D-carnitine, and L-Carnitine is its active type. The average human body contains 20 to 25 grams of L-Carnitine 95 percent of which is found in skeletal muscle and myocardium (Horleys, 2003). Carnitine was first isolated from bovine muscle in 1905 and the word carnitine is a derivative of the Latin root "carnis" meaning meat. Its significance in oxidation of fat was identified for the first time in 1950 (Timothy, 2002). Since then the role of loading of this amino acid in some diseases and healthy individuals has been identified. The bodies of humans and other mammals are able to synthesize carnitine endogenously some amino acids. So in humans and other mammals it is both absorbed through the diet (75 percent) and synthesized from the essential amino acids lysine and methionine and Vitamin C precursors, Niacin, vitamin B And iron by the liver and kidney and it is then stored in skeletal muscle, heart, brain and sperm (Horleys, 2003).

Carnitine is abundantly available in meat and animal products, poultry, fish and in smaller amounts in milk and dairy products and in very tiny amounts in herbal foods (Arenas *et al.,* 1998). Hence, those with inadequate daily intake of red meat and animal products have small reserves of carnitine. However, carnitine defects or deficiency occurs rarely even in persons following a vegetarian diet because the healthy human body is capable of producing sufficient carnitine from its precursors. In people whose diets contain mostly plant sources, about 90 percent of carnitine is synthesized in the body (Rebouche, 1992). Meat in adults and mother's milk in childhood are the main sources of carnitine (Rebouche, 1992).

Carnitine Metabolism and Biochemistry

Daily intake of 150 to 500 Mmol (24 Up to 81 Mg) Carnitine is sufficient in the adult body. Mucosal absorption of 2 grams a day is saturated (Harper *et al.,* 1992). Physiologic carnitine uptake is done by active transport and its pharmacological absorption is done by passive diffusion (Li *et al.,* 1995). Researchers recognize that in different tissues of an organism there is a transmission interface that uses extracellular sodium outside as a cotransporter ion. Distribution of L - Carnitine into tissue has a half-life of 2 to 3 hours (Brass, 1995). Most of body L-carnitine reserves are in skeletal muscle and heart (95 Percent) and the remaining 5 Percent are reserved in the kidney, liver, other tissues and extracellular fluids. Higher levels of carnitine in skeletal muscle and heart increase oxidative metabolism of fatty acids in these tissues. Physical activity and exercise, especially vigorous aerobic exercise reduces the body total L-Carnitine concentration, however, there is no unanimous (Timothy, 2002).

Carnitine concentration in humans depends on age and sex. Human plasma carnitine concentration increases from 15 to 40 Mmol per liter in the first years of life and remains constant equally in both sexes until (Giannacopoulou *et al.,* 1998). Then From puberty to adulthood, men carnitine concentration increases and then remains constant at a certain level which is significantly higher than that of women (Mmol 50 against mmol 40) (Takiyama et al., 1998). This suggests that male sex hormones are involved in plasma carnitine concentration (Fredric *et al.,* 2002). Thyroxin and thyroid hormones increase hepatic carnitine levels. Intake of thyroxin doubles hepatic carnitine concentration in rabbits (Pande *et al.,* 1980). Researchers have found that after oral supplementation of 2 grams of L-Carnitine, plasma

carnitine levels in healthy subjects would increase up to 69 Mmol per liter (Timothy, 2002).

If the concentration of plasma carnitine exceeds its maximum reuptake or transfer, excessive carnitine is excreted through urination (Heidrum *et al.,* 2004). Carnitine is released in large quantities through renal excretion, but it is significantly reabsorbed by the kidneys (Engel *et al.,* 1981; Rebouche *et al.,* 1993). L-carnitine compound us freely filtered in renal glomeruli and more than 90 percent of filtered carnitine is reabsorbed in the opening renal tubules and when plasma carnitine level is normal or less, it finds its way to blood circulation (Heinonen, 1996). Thus, when the levels of plasma carnitine increase due to supplementation, its reuptake decreases and it is excreted in large quantities through urination. Hyperthyroidism increases and hypothyroidism decreases urinary excretion of carnitine. Indeed, there is a complex metabolic balance between different components of carnitine in the different parts of the body as well as between carnitine levels of tissues blood. Daily renal excretion of carnitine is 15 to 50 Mg (Heinonen, 1996). Half-life of human plasma carnitine is about 2 to 15 hours. L-Carnitine can also cross through the placenta and it can be released through mammary glands milk. Neonatal period foods are often strengthened L-Carnitine, because dairy proteins are generally are considered poor sources of L-Carnitine precursor amino acids, and children have a low capacity for synthesis of L-Carnitine (Heidrum *et al.,* 2004).

Carnitine plays an essential role in energy production by controlling the entry of long-chain fatty acids into mitochondria (Bremer, 1983). Long-chain fatty acid that is the preferred substrate for muscular energy production does not freely enter the mitochondrial membrane, but when combined with coenzyme A it converts to long-chain acyl-CoA and the resulting acyl co A loses its CoA after combining with L-Carnitine and converts to acyl carnitine CoA and then the long chain fatty acid easily enter into the mitochondria (Bremer, 1983). When L-Carnitine is not sufficiently available in the body (especially in congenital carnitine deficiency syndromes), the reduced fatty acid enters into mitochondria and leads to insufficient energy production and fatty acid accumulates in the cytoplasm or outside the mitochondria and causes toxic effects (Timothy, 2002). Recently L-Carnitine has been identified as a metabolic antioxidant (Didonato *et al.,* 1992).

Pharmacokinetic significance of L-Carnitine

When L-Carnitine enters into the body through diet it is easily absorbed in the duodenum and ileum. Then it enters through portal veins into the liver and eventually enters the blood stream (Timothy, 2002). Maximum absorption of plasma L-carnitine occurs 3 to 5 hours after supplementation. Some reports state that obesity is associated with higher levels of plasma carnitine but the importance of these findings is still unknown (Engel *et al.,* 1981). Some people suffer from genetic carnitine defects or carnitine diet deficiency or are not capable of absorb it exogenously. Carnitine deficiency can be caused by various genetic disorders and associated with hepatic and renal diseases, hemodialysis, diabetes, hepatic cirrhosis, metabolic irregularities, high fat diet, uncontrolled consumption some medications and low levels of lysine and methionine amino acids in the diet. Carnitine deficiency in human may be hereditary or acquired. Hereditary carnitine deficiency manifests in myopathic, systematic and organic acid resistance forms (Tanphichitr *et al.,* 1992). Among carnitine deficiency symptoms are fatigue, chest pain, muscle pain, general weakness, low blood pressure and dizziness. Acetyl carnitine deficiency diagnosis is based on free carnitine levels in serum, urine and tissue (Tanphichitr *et al.,* 1992). Carnitine deficiency syndrome leads to impaired or inefficient metabolism of fatty acid in muscle or heart. L-Carnitine supplementation is useful for individuals with carnitine deficiency or for those whose diet has been

confirmed to be of inadequate carnitine (Arsenian, 1997). Discontinued or reduced consumption of carnitine in renal diseases are alarming but any carnitine supplementation in dialysis patients may be harmful without a physician's diagnosis and consultation. Little study has been conducted on the effectiveness or usefulness of carnitine in improvement of hemodialysis patients. Brass et al have reported beneficial effects of carnitine supplementation on cardiovascular patients (Hill, 1995).

Carnitine and Cardiovascular Disease

Reduced levels of free carnitine levels in cardiac patients are more obvious than in healthy individuals. Normal function of heart muscle is significantly dependent on the lipid oxidation. Failure of this substrate in lipids oxidation has been reported in patients with ischemia. Using animal models, researchers have reported the ability of L-Carnitine in reducing the incidence of cardiac arrhythmia in ischemic patients (Moslem *et al.,* 2010). A 12-week L-Carnitine supplementation in patients with congestive heart failure led to increased exercise tolerance. This substance is also a positive therapeutic agent on hyperemic heart disease compared with traditional medicines. Angina pectoris develops due to inadequate delivery of oxygen to the heart muscle. Japanese researchers have shown that consumption 900 grams of L-Carnitine in 12 Angina patients has led to increased exercise tolerance (Kamikawa *et al.,* 1984). Isolated rabbit heart with Carnitine deficiency, revealed a 60-percent decrease of their cardiac carnitine compared with healthy rabbits. In an animal study, intravenous administration of L-carnitine led to increased cardiac ATP density storage and natural function of cardiac metabolism in ischemic dogs (Timothy, 2002). L-Carnitine supplementation in animals has beneficial hemodynamic effects. Intravenous administration of L-carnitine increased myocardial contractility by 35% Shrinkage and decreased heart rate by 17% and showed direct effect on dilation of coronary arteries, and these changes led to a 60-percentage increase in the blood flow in coronary arteries (Timothy, 2002). Scientific studies have proven a one-year treatment of 2500 patients with coronary artery disease with L-carnitine in prevalence of angina and the need for cardiac drugs (Singh *et al.,* 1998). The observed effects of L-Carnitine on myocardial metabolism are independent of catecholamines. Intravenous administration of L-carnitine in humans is now common. In a study on 56 patients with acute myocardial infarction, intravenous injection of L-carnitine considerably reduced arrhythmia (Timothy, 2002). Also in another study on MI patients, a daily supplement of 2 grams of L-carnitine for a period of 28 days noticeably reduced different symptoms of heart disease such as infarction intensity, Lipid peroxides enzyme concentrations and serum aspartate transaminase and on the other group the same amount of loading led to reduced angina pectoris, heart failure, arrhythmias and reduced pathological left ventricular hypertrophy in patients with a history of acute heart attack (Timothy, 2002). Daily intake of 1.5 grams of L- carnitine for 3 Months in patients with congestive heart failure, led to improved administration fraction (EF) of the left ventricular and alleviated breathlessness. Background researches indicate that longer treatments of cardiac patients would be more compatible with consumption of L-carnitine (Brevetti *et al.,* 1988). In this context, consumption of 500 mg L-carnitine twice a day by patients with congestive heart failure after 30, 90 and 180 days of supplementation led respectively to 16.4% , 22.9% and 25.9% increase in exercise tolerance and 8.4% , 11.6% and 13.6% And increase in let ventricular administration fraction (Brevetti *et al.,* 1988). Daily intake of 500 mg L-carnitine Propionyl for 6 months led to a 26-percent increase in exercise capacity. Also carnitine supplementation in patients with congenital carnitine deficiency syndrome increases their cardiac function (Mancini *et al.,* 1992).

Carnitine and Alzheimer's disease

Clinical studies emphasize that Acetyl - L-carnitine that is ester of acetyl L-carnitine derived from L-carnitine and acetyl groups, has beneficial effects in depression abnormalities and Alzheimer's disease and delayed progression of this disease, improved memory or relative inhibition of dementia in old age (Bianchetti *et al.,* 2003). Experimental researches have indicated significant reduction in carnitine acetyl transferase through autopsies on Alzheimer's patients (Arsenian, 1997). Acetyl section develops from acetyl L-carnitine to form neurotransmitter acetylcholine. Abnormal metabolism of acetylcholine in the brain causes acetylcholine defect in certain brain regions that is associated with decreasing age and Alzheimer's disease (Brook *et al.,* 1998). Pharmacokinetics studies have well revealed acetyl-L-Carnitine's ability to cross the blood–brain barrier in Alzheimer's patients (Parnetti *et al.,* 1992). In this context the daily intake of 1.5 grams of L-carnitine three times a day, for a period of 50 days by eleven Alzheimer patients, significantly increased concentrations of L-carnitine and acetyl L-carnitine in plasma and cerebrospinal fluid which is indicative of these substances crossing blood-brain barrier. However, research findings about the beneficial effects of carnitine on Alzheimer's disease and memory improvement are more of less contradictory. For example, a research study indicated that consumption of L-carnitine in the early stages of Alzheimer's disease would improve progression of this disease, but in later stages of the disease it would aggravate it (Arsenian, 1997). Also daily intake of 3 grams of L- carnitine for 60 days by elderly subjects (aged 60 to 80) with depressive illness significantly decreased depressive symptoms against placebo group (Yousry, 2000). It seems that young Alzheimer's patients are more receptive to the beneficial effects of acetyl L-carnitine supplementation. However, L-carnitine for patients with Alzheimer's disease and other forms of it must be consumed under supervision of a specialist physician (Brook *et al.,* 1998).

Carnitine and other diseases

Researchers recommend L-Carnitine supplementation in certain conditions and diseases a summary of which is presented in Table 2. Chronic hemodialysis occurs following anemia, hypertension and decreased body fluids. Carnitine depletion or decreased plasma carnitine levels down to 50 percent is accompanied with the said consequences. Daily intake of 1 gram of L-Carnitine for one month followed by daily intake of half a gram of L-Carnitine for one month by 11 hemodialysis patients effectively increased plasma carnitine and increased intake of fatty acid in heart tissue (Timothy, 2002).

The formation of free radicals, which is the consequence of vigorous exercise or some diseases, has deleterious effects on cellular components, especially mitochondria DNA and mitochondria lysosomes and walls, and would probably result in cancers of lung, skin, stomach and prostate or activation of cell destructive enzymes and hardening of the arteries walls (Cerretelli *et al.,* 1993). Recently most studies have confirmed the protective role of carnitine and its ester acyls in the body especially the mitochondria in refining toxic substances such as free radicals (Horleys, 2003). Acyl carnitine accumulation is high in patients with chronic renal disease. Decreased renal function and acyl carnitine accumulation on the synthesis of carnitine in the kidneys of these patients is alarming. Muscle carnitine levels are reversely correlated with the duration of dialysis disease and are directly correlated with the peak of ability of body muscles to absorb oxygen in hemodialysis patients during exercise. Intravenous carnitine administration is highly important in increasing muscle total carnitine content in these patients. Daily intake of 20 mg/kg of L-carnitine for a period of 6 months by dialysis patients

increased their performance capacity by 11 percent (Eric *et al.,* 1998).

In patients with type II diabetes, intravenous administration of L-Carnitine (45 Micrograms per kilogram of body weight) led to increased insulin sensitivity and decreased levels of lactic acid (Timothy, 2002). Peripheral nerves function of diabetic and the cerebral blood flow in cerebrovascular patients improves by using acetyl L-carnitine (Brook *et al.,* 1998).

Researchers recommend taking L-carnitine to reduce septic shock and chronic fatigue syndrome (Timothy, 2002). In fact shock represents circulatory system failure and its key feature is inadequate blood flow to body tissues. Administration of L-carnitine has been reported beneficial in treatment of shock induced by weight loss, heart attack or severe infection of vessel. Acetyl-L-carnitine intake accelerated healing of infection and cardiogenic shock in 115 of these patients (Arsenian, 1997).

Some biochemical changes such as the synthesis of cardiolipin, which is a key phospholipid in fatty acid transport process in heart mitochondria for energy production, decreases by aging in adulthood and old age which leads to impaired functioning of heart mitochondria. A study on older rabbits revealed that loading acetyl L-carnitine leads to improved mitochondrial function and increased cardiolipin production (Brook *et al.,* 1998).

Researchers believe that poor nutrition and carnitine deficiency are among significant causes of chronic fatigue syndrome. A study on 30 subjects with chronic fatigue syndrome indicates that that L-carnitine supplementation, especially after 4 to 8 weeks of consumption brings about better results than taking other drugs dealing with fatigue (Eric *et al.,* 2002).
The beneficial intake of L-carnitine has also been reported in chronic lung diseases. The intake of 2 grams of carnitine, twice a day for 2 to 4 weeks led to positive changes of respiratory response to exercise in these patients. (Dal *et al.,* 1998).

Low level of sperm in men is associated with low levels of carnitine and carnitine loading in infertile men improves sperm proliferation and motility and their fertility. Supplementation of 3 grams of L-carnitine for three months tangibly increased sperm concentration (Brevetti *et al.,* 1988). Also daily intake of one gram of L-carnitine for 6 months significantly increased sperm fertility in men with unknown fertility disabilities (Timothy, 2002). Acetyl L-carnitine is loaded for use in respiratory and reproductive process of spermatozoa (sperm cells). Significant improvement in visual accuracy and memory in patients with Down syndrome has been reported with the use of acetyl L-carnitine (Brook *et al.,* 1998).

Alcohol reduces the body's carnitine function ability. It leads to fatty liver or increases development of fatty liver. Animal studies have shown that carnitine supplementation prevents increased risk of fatty liver caused by alcohol consumption. Studies have shown that the levels of amino acids such as carnitine are reduced in subjects with anorexia nervosa. Subjects with nutritional disorders with low level of carnitine also suffer from muscle weakness. Study on lean women with anorexia nervosa showed that carnitine supplementation resulted in increase of this amino acid or leads to improvement of muscle weakness. If an individual suffers from anorexia nervosa, a specialist physician is to determine the necessity of carnitine intake. Physicians believe that prescription of L-carnitine is useful in inhibition or mitigation of the symptoms of hyperthyroidism. These symptoms manifest in forms of increased heart rate, insomnia, nervousness or tremor. Carnitine intake by hyperthyroidism patients led to improvement of these symptoms and normalization of their body temperature (Arsenian, 1997).

In general, carnitine has a significant impact on consumption of fat and to burning fatty acids. The burning process of fatty acids is directly correlated with the reducibility of total cholesterol and LDL cholesterol and at the same time increases HDL cholesterol. Carnitine's role has been proved in reducing particularly coronary artery stenosis and the risk of vascular occlusion (McMackin *et al.,* 2007). Studies in this area are indicative of beneficial impacts of L-carnitine. In a certain study, after 4 months of carnitine therapy, total cholesterol and triglyceride levels, decreased respectively by 20 and 28 percent and HDL cholesterol concentration increased by 12% (Brevetti *et al.,* 1988). Meanwhile, triglyceride and HDL cholesterol show greater sensitivity in reaction to carnitine supplementation.

Italian researchers (Journal of Urology 2004) suggest that carnitine and testosterone have matching effects in improving symptoms of aging such as sexual dysfunction and depression associated with reduced androgens. In a research, 120 elderly men aged 60 to 70 with low testosterone symptoms were placed in Group A: 160 mg of testosterone daily, Group B: 2 grams of L-carnitine Propionyl daily together with 2 grams of acetyl L-carnitine, Group C: placebo group. Sexual function, sexual desire and sexual gratification increase similarly in Groups A and B. Treatment with testosterone increased free testosterone and serum total testosterone and decreased levels of luteinizing stimulator hormone (Matsumura *et al.,* 1998). But Carnitine's effects on these hormones were not significant. But, although the improvement of certain factors with carnitine was not equivalent with that with testosterone carnitine therapy did not cause side effects like prostate enlargement that is a consequence of treatment with testosterone (Matsumura *et al.,* 1998).

Peripheral vascular disease is caused by arteriosclerosis of the arteries of lower extremity that is marked with blood flow to the legs. This disease is associated with severely limited exercise capacity, spasm and irritation in legs while walking or physical activity as ischemic pain in leg muscles. Scientific evidence suggests that chronic ischemia in peripheral vascular disease leads to multiple metabolic changes in the leg muscles as well as acyl carnitine accumulation (Janssen *et al.,* 1998). The study of Brutti et al about the beneficial effects of carnitine therapy (2 grams, twice a day for 3 months) on these patients significantly improved their exercise performance. The same beneficial effects have also been reported following intravenous administration of carnitine. In another study, after three weeks of L-carnitine and Propionyl L-carnitine supplementation, the length of hiking in the therapy group turned out to be 75% more than that of placebo group. Of course, it is rather difficult to understand the pharmacological importance of carnitine in these patients. Propionyl L-carnitine that is a kind of L-carnitine is more effective in improving muscle metabolism in peripheral vascular disease. Propionyl L-carnitine converts to carnitine and Propionyl CoA in the tissue which is highly significant in carnitine availability and the supply of Propionyl as a complementary substrate (DiLisa *et al.,* 1989) (Krebs cycle mediator for continuity of the cycle's function) for completion of oxidation of fuel substrates. Propionyl L-carnitine (PLC) supplementation and placebo (2 grams per day for 6 months) on 155 subjects with peripheral vascular disease, increased the time of exercise test in the placebo group by 25%, while the increase in PLC Group was 54 percent (Eric *et al.,* 1998). This study supports the potential effectiveness of carnitine and L-propionyl carnitine in these patients.

Carnitine effects on hematopoiesis

In hemodialysis patients taking L-carnitine increases hematocrit and improves erythropoietin response and is effective in the function of erythrocytes in increase of haematopoiesis and increased erythropoietin activity leads to further stimulation of mother hematopoietic stem cells that produce red blood cells. While renal

anemia can be successfully treated in dialysis patients by administering erythropoietin, some of these patients show long latency periods in treatment with erythropoietin. Laboratory researches indicate the stimulatory effect of palmitoyl-L-carnitine on erythropoietin in haematopoiesis of these patients (Matsumura *et al.,* 1998). The daily intake of 500 mg of L-carnitine for a period of three months by patients who had previously responded poorly to erythropoietin significantly increased hematocrit and the capacity of total iron and significantly decreased ferritin (Matsumura *et al.,* 1998; Kitamura *et al.,* 2005). The administration of 12.5 micromole of palmitoyl L-carnitine with erythropoietin to mouse liver cells significantly increased red blood cells (Matsomoto etal., 2001). The study of Matsumara indicates another aspect of effectiveness of L-carnitine supplementation on erythropoietin capability when dwelling in elevation or under hypoxic conditions (Matsumura *et al.,* 1998).

Proposed Values of L-carnitine (Arsenian, 1997)

- Fat metabolism and muscle function: 1000 to 2000 mg, twice a day
- Heart disease: (600 to 1200 mg, three times daily) or (750 mg, twice daily)
- Alcohol carnitine deficiency: 300 mg, three times a day
- Male Infertility: 300 to 1000 mg, three times daily
- Chronic fatigue syndrome: 500 to 1000 mg, three to four times a day
- Over active thyroid (hyperthyroidism): 2000 to 4000 mg in two to four times a day.

Carnitine, weight loss and exercise performance

Weight loss or weight control is one of the major objectives of advanced human societies to gain better health and further comfort. Researchers suggest that a dynamic lifestyle that could lead to increased uptake of fat reserves is the first steps toward weight loss (Heidrum *et al.,* 2004). Because of the essential role that carnitine plays in lipid metabolism, is a weight loss nutritious substance favorable together with physical activity and diet. In fact, carnitine supplementation increases fat oxidation which increases burning of fat reserves in thighs, abdomen and other tissues of the body. However, some studies have shown that oral intake of carnitine (6 grams a day for 14 days) causes no change in muscle carnitine concentrations in healthy non-obese subjects nor does it cause weight loss (Heidrum *et al.,* 2004). This evidence is inconsistent with other clinical studies supporting the beneficial effects of carnitine supplementation in reducing weight. Recent research data suggest that high doses of L-carnitine stimulate glucocorticoid receptors and trigger some biological activities of glucocorticoid, which in turn is a factor for the stimulation of adipose tissues lipolysis. Also it should be noted that Etomoxir, an inhibitor of carnitine Palmitoyl transferase decreases body fat oxidation and anticonvulsants that decrease carnitine enables weight gain (Heidrum *et al.,* 2004).

In a study, the weight loss effect of taking L-carnitine was analyzed on students aged 13 to 17. Both experimental and placebo groups had similar diet, and volume of physical activity, with the exception that the experimental group took grams of L-carnitine on a daily basis (Daniel, 2001). In the end weight loss in the placebo group was 1.5 lb, but weight loss in the experimental group was 11 Pound (Daniel, 2001). Also Gilbert Kats et al (1992) evaluated weight in 23 men and women aged 19 to 65 in two 8-week programs; one without supplementation and one with daily supplementation of 200 mg of L-carnitine. At the end of the first 8-week stage, there was no weight loss, no blood cholesterol reeducation and no change in resting energy expenditure, but after the second 8 weeks, there was an 11-pound reduction in the body fat, 11 percent reduction of blood cholesterol and 9 percent decrease in LDL cholesterol, but there were no changes the body fat mass and resting metabolic expenditure (Daniel, 2001). Moreover, weight loss in the experimental group did not bring about any harmful side effects.

This study clearly demonstrates the effect of carnitine supplementation on weight loss. Of course in the first days, it is better to take carnitine, preferably before or during the breakfast.

L-carnitine supplementation has become prevalent among athletes in recent years. L-carnitine supplementation relies on two pre-assumptions: a) it increases fat consumption by active muscles which facilitates glycogen storage and consequently results in longer exercise performance and delayed fatigue, b) it facilitates homeostasis of esterified L-carnitine and free in the muscle and plasma (Robert, 1998). Researchers believe that in addition to muscle energy production, L-carnitine intake has scientific application for sports coaches and physiologists (Soop *et al.,* 1998). Although carnitine is synthesized in the body and is also absorbed from the diet, in some circumstances, L-carnitine supplemental has been reported beneficial especially by cyclists and endurance runners among whom muscle carnitine deficiency is possible (Harper *et al.,* 1998, Horleys, 2003). Most studies support the beneficial effects of carnitine. In an overall review, the beneficial effects of L-carnitine on exercise performance in 14 studies including 305 subjects were confirmed and no adverse side effects were reported (Heidrum *et al.,* 2004). Intake of 2 grams of carnitine daily increased the running speed of athletes by 5.5 percent and in untrained subjects it led to endurance performance somewhat close to athletes (Robert, 1998). Daily supplementation of 5 grams L-carnitine for five days reduced heart rate during the cycling by 7 to 8%, which shows improvement in cardiovascular performance during sub-maximal exercise (Soop *et al.,* 1998). The protective effect of L-carnitine is of particular importance on blood cells, particularly the platelets which play blood coagulation and regeneration role against muscular traumas caused by exercise. L-carnitine is clearly effective on the increase of blood by-products and results in amplified intake of oxygen and other nutrients in particular during exercise (Heidrum *et al.,* 2004). The review study of Matera et al also demonstrated that reduced lactate production during exercise is another function of L-Carnitine supplementation (Matera, 2003). But, a recent study showed that L-carnitine supplementation had no significant effect on free fatty acide and lactate concentration and maximal oxygen concumption (VO2max) during submaximal exercise (Eizadi[a] *et al.,* 2011).

One of the severe consequences of physical activity is drop in oxygen (HYPOXIC) that is followed by increase in blood ammonia concentration. Ammonia and blood lactate accumulation strongly depends on exercise intensity (Heidrum *et al.,* 2004). Carnitine administration in laboratory rodents prevents ammonia intoxication during exercise under hypoxic conditions through three mechanisms: (a) - activating enzymes in the urea cycle, B - reaction with glutamate receptors, C - Reduction of free radicals. On the other hand, supplementation of carnitine (three grams per day for three weeks) helps reduce muscle soreness (Giamberardino, 1996). Heidrum show that carnitine relatively inhibits purines catabolism, formation of free radicals, and degradation of sarcolemmal and delayed contusion (Heidrum *et al.,* 2004). In contrast, some studies corroborate lack of any significant changes in blood glucose concentration and carbohydrate oxidation (Rantzau *et al.,* 2008). the findings of a recent study showed that L-carnitine supplementation does not affect fat-carbohydrate metabolism and aerobic capacity in young students during cycling exercise (Eizadi[b] *et al.,* 2011).

Carnitine allowable values and safe:

Accurate calculation of pharmacological or supplemental use of carnitine in healthy individuals or in different disease conditions is rather difficult, because this substance is synthesized through the diet and endogenously in the body. L-carnitine is recommended to taken with food (Horleys, 2003). No negative side effects has been reported for the pharmacological or supplemental use of L-

carnitine in human or other animal species indicative of mortality even in cases of high dose consumption. Supplementation of 2 grams of L-carnitine for a period of one year in more than 4000 patients revealed that only 6 percent of the subjects suffered from to mild stomach discomfort, 5% suffered from nausea and 2% from diarrhea (Timothy, 2002). Except in dialysis patients, clinical doses of carnitine are 48 to 350 mg per day per each kilogram of per body weight. With regard to these findings from a pharmaceutical viewpoint, the lowest effective amount of carnitine in healthy subjects has been estimated to be 3 to 3.5 g per day (Arsenian, 1997). However, it seems that long-term use at the daily dose of 2 grams is appropriate. Acetyl-L-carnitine intake by pregnant women and nursing mothers is not recommended due to lack of long-term studies in this field (Brooks *et al.,* 1998).

Conclusion

Carnitine nitrogen compound in skeletal muscle and myocard facilitates oxidation of free fatty acids. The major part of excessive carnitine is renally excreted at the rate of 15 to 50 mg so a haemostatic balance is constantly maintained between glomerular reuptake and renal tubular and the plasma level of carnitine. Mammals are able to synthesize endogenously carnitine from methionine and lysine vital amino acids. Scientific evidence indicates that plasma or endobiotic concentration of carnitine decreases in proportion to disease type and is followed by slowed fat oxidation process in the heart. While intravenous L-carnitine administration results in positive effect on Myocardial contractility, heart stroke volume, cardiac output and reduced side effects after a heart attack, such as severe infarction, cardiac arrhythmia and ischemia. It also increases insulin sensitivity in diabetic patients and leads to improved blood flow in brain arteries. Research findings confirm the beneficial effects of oral and intravenous carnitine in hemodialysis patients and patients with chronic pulmonary disease and carnitine deficiency syndrome. It is also useful for spermatozoa fertility, increase of accuracy and memory in Down syndrome patients as well as weight reduction. Appropriate use of carnitine as medication has been reported to be free of any serious side effects even for prolonged periods.

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