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Review Article

CARNITINE, METABOLISM, SUPPLEMENTATION AND EXERCISE PERFORMANCE

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ABSTRACT
Carnitine is an important cofactor in fat catabolism as a source of energy. This substance is both available in the diet and is made in the liver and kidneys from lysine and methionine precursors. The internal synthesis routes of carnitine seem to be sufficient to meet body needs. It is well established that in case of Carnitine deficiency, L-carnitine loading adjusts long chain fatty acid metabolism and their entry into the mitochondria. However, its role in long chain fatty acid metabolism in people without fat metabolism disorder is not yet clear. In addition L-carnitine has a potential effect on exercise capacity and activation of branched amino acid oxidation and stimulation of pyruvate dehydrogenase complex. Athletes consume L-carnitine under the illusion that it would enhance athletic performance and delay fatigue as a result of stimulation of fat oxidation and glycogen storage.

INTRODUCTION
Background and Identification of carnitine
Carnitine was first isolated from bovine muscle in 1905 and the word carnitine is a derivative of the Latin root "carnis" meaning meat. Then in 1927 its chemical structure was identified as L-carnitine or (3 Hydroxy - 4 - amino methyl butyrate). In 1950 Urwin Fritz discovered that carnitine was involved in the oxidation of long chain fatty acids (LCFA) in the myocardium and other muscles, and later the role of the derivatives of this amino acid (L-carnitine, D-carnitine, acetyl-L-carnitine, Propionyl-L-carnitine) and its supplementation it in some diseases as well as healthy individuals controls was identified (Maher , 2001).
Food sources and the endogenous synthesis of carnitine
The bodies of humans and other mammals are able to synthesize endogenously carnitine from certain amino acids. Carnitine is synthesized by two essential amino acids; lysine and methionine particularly by the liver and the kidneys and it is stored in the skeletal muscle, heart, brain, sperms and other tissues that capable of oxidation of fatty acids. Formation of this substance needs such cofactors as vitamin C, Niacin, vitamin B and iron. In addition dietary intake of carnitine is done to maintain its reserves. In fact, 75 percent of carnitine required by the body enters the body through the diet. Red meat, poultry, fish and dairy products are considered the main sources of carnitine. Meat in adults and human milk in childhood are the main sources of carnitine. Therefore, persons with inadequate daily intake of red meat or dairy products have less reserves of carnitine. Plant foods contain smaller amounts of carnitine than animal foods. However, carnitine deficiency also occurs less frequently in these individuals. Since the healthy human body is able to produce enough of carnitine from its pre-structures. Generally, in people whose diets contain mostly plant sources, about 90 percent of carnitine synthesis is of endogenous origin (Horleys, 2003)
Metabolism and excretion of carnitine
The adult body contains on the average 25 grams of L-carnitine. Daily intake of 150 to 500 mmol (24 to 81 mg) is sufficient in adults. Maximum mucosal absorption is estimated to be 2 grams per day (Natali, 1993). Pharmacologic and physiological carnitine uptake is done through active transfer and passive permeation (Li *et al.,* 1992). L-carnitine transfer is done in different tissues of the body supported by a transfer intermediary that uses the extracellular sodium as the cotransporter ion. Distribution of L-carnitine in the tissue has the half-life of 2 to 3 hours (Brass, 2000). Concentration of L-carnitine in tissues is usually several times higher than its concentration in plasma. Concentration of skeletal muscle L-carnitine is approximately 70 times the plasma concentration. The most reserves of L-carnitine in the body are skeletal muscles and heart (95%) and about 4% in the kidney, liver and other tissues and

remaining one percent is in extracellular fluids. The larger mass of carnitine in skeletal muscles and heart speeds up oxidative metabolism of fatty acids in these tissues. Liver and brain have receptors with low capability of carnitine uptake while carnitine uptake in the renal tubules and gastric epithelial cells is rapid. Physical activity, especially intense aerobic exercise, reduces the total concentration of body L-carnitine (Timothy, 2002).

Carnitine concentration is dependent age and sex. Plasma carnitine concentration during the first years of life increases from 15 to 40 Mmol per liter in the size remains constant in both sexes until the age of puberty. But from puberty to adulthood, men's carnitine concentration increases and then remains constant at a sustainable level. Carnitine reserves are far greater in men than in women. This signifies the role of male sex hormones in the levels of plasma carnitine (Fredric *et al.,* 2002). Thyroxin and thyroid hormones increase hepatic carnitine levels. Scientific evidence report doubled hepatic carnitine concentrations in mice after taking up thyroxin. The impact of sex hormones, pituitary hormones, Insulin and glucagon (Fredric *et al.,* 2002) on carnitine levels is remarkable. But their direct impacts on the biosynthesis of carnitine have been studied less. Researchers have found that in healthy subjects after supplementation of 2 g L-carnitine, the plasma levels increased on the average to 69 mmol/L (Maher , 2001).

If the plasma carnitine concentration exceeds that of its maximum reuptake (more than 60 to 100 mill moles per liter of plasma) the excess amount is excreted through the urine (Horleys, 2003; Brass, 2000). Although carnitine is released through in large volumes through renal excretion, a considerable amount of carnitine is reabsorbed by the kidneys. L-carnitine is purified freely in renal glomerulus and more than 90 percent of the filtered amount is reabsorbed in primary renal tubules and when plasma carnitine levels are normal or lower it enters blood circulation. Thus, when the levels of plasma carnitine increase following supplementation, its uptake decreases and a considerable amount of it is excreted. However, the hypothyroidism complication increases the urinary carnitine excretion and hypothyroidism decreases its urinary excretion. In fact, there is a complex metabolic balance between different components of carnitine in different parts of the body and carnitine levels in tissues and blood. The daily urinary excretion of carnitine is 15 to 50 mg.

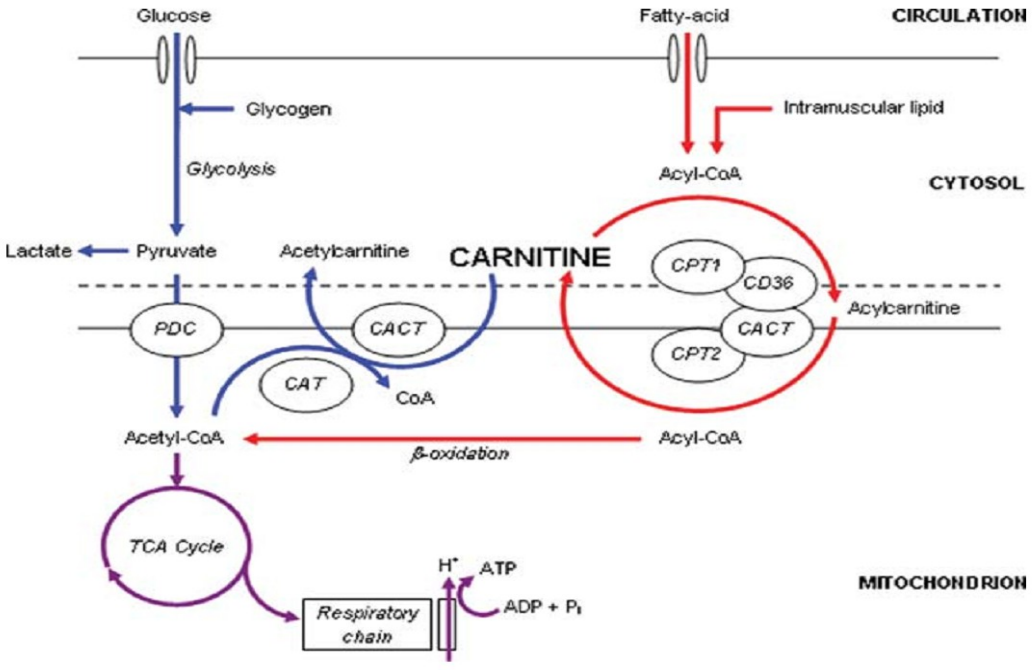

Figure 1. A schematic diagram of the metabolic roles of carnitine in skeletal muscle
Carnitine's role in long-chain fatty acid (acyl group) translocation into the mitochondrial matrix, for subsequent β-oxidation is highlighted in red, whereas the role of carnitine as a buffer of excess acetyl-CoA production is highlighted in blue. PDC, pyruvate dehydrogenase complex; TCA, tricarboxylic acid cycle; CAT, carnitine acetyltransferase; CACT, carnitine acylcarnitine translocase; CPT, carnitine palmitoyltransferase; CD36, fatty acid translocase.

Biochemistry of L-carnitine

Long-chain fatty acid is transferred into the mitochondrial membrane for energy production purposes through the beta-oxidation process. This compound is the preferred substrate for energy production in muscle which can not find its way freely to the mitochondrial membrane. However, after combining with Coenzyme A it converts to Acyl co A with long-chain and after combining with carnitine, Acyl CoA is converted to acetyl carnitine and in form of acetyl-carnitine the long chain fatty acid easily enters the mitochondria (Fig. 1, Francis *et al.,* 2007).

Acetyl-carnitine inside the mitochondria reconverts to acyl-CoA and L-carnitine. Then L-carnitine finds its way out of the mitochondria and starts operating to participate in remobilization and acyl CoA enters Krebs cycle for beta-oxidation process (Maher , 2001). Also in addition to transporting fatty acid into mitochondria, carnitine facilitates oxidation of branched Keto acids and by inhibiting their accumulation supports cellular protection of the accumulation of Acyl CoA (Joaquin *et al.,* 1994).

Carnitine palmitoyltransferase Type 1 and 2 (CPT_1, CPT_2) are replaced in the outer and inner mitochondrial membranes. CPT 1 perpetrates the highest stimulatory effect and mitochondrial beta-oxidation speed control. Malonyl-CoA, the first mediator precursor of fatty acid biosynthesis, is an effective physiological inhibitor of carnitine palmitoyltransferase Type 1. When there is adequate ATP available, additional acyl CoA of Krebs cycle path changes its path and heads for Malonyl-CoA. Hence catabolism of fatty acids decreases and accelerates development of and fatty acids and synthesis of triglyceride. So there is always a reciprocated equilibrium of fatty acid oxidation and biosynthesis maintained by carnitine and Malonyl-CoA under normal and ketonic circumstances. When, as a result of carbohydrate-rich diet, the ratio of plasma glucagon to insulin decreases, Malonyl-CoA concentration increases and the synthesis of fatty acid increases and fatty acid oxidation rate decreases at the same time. Conversely, in conditions of hunger and fasting or diabetes when the ratio of plasma insulin to glucagon is high, the levels of Malonyl-CoA decrease and hepatic carnitine levels increase. This transformation leads to a decrease in fatty acid synthesis. As a result Carnitine palmitoyltransferase is stimulated to facilitate fatty acid oxidation and Ketogenesis (Joaquin *et al.,* 1994). When L-carnitine is not sufficiently available in the body (especially in congenital carnitine deficiency diseases), its decrease causes less fatty acid to enter into mitochondria and leads to lower inadequate beta-oxidation energy production, and fatty acid accumulates in the cytoplasm or outside the mitochondria and creates toxic effects (Maher , 2001). Recently L-carnitine has been identified as a metabolic anti-oxidant (Joaquin *et al.,* 1994).

The impact of L-carnitine on exercise performance

Athletes are often vulnerable to temptation of taking supplements to improve their weak athletic performance and use different feeding methods, such as carbohydrate loading which has beneficial effects (Sherman *et al.,* 1981). Although carnitine is synthesized in the body and it is also absorbed into the body from the diet, in certain circumstances, in competitive athletes and in intense endurance activities where there is the possibility of muscle carnitine deficiency, supplementation of L-carnitine is beneficial (Horleys, 2003). L-carnitine was listed as a possibly doping substance in 1982. This coincided with the time when the Italian national football team became the World Cup champion, and they had used this supplement (Natali, 1993). Today, L-carnitine is consumed in most countries that believe in the positive effect of its supplementation on athletic performance. Recently, L-carnitine was removed by the International Olympic Committee from the list of banned doping substances; because this substance is naturally and abundantly absorbed with the diet (Horleys, 2003).

Carnitine has a key role in three bio-energy reactions of skeletal muscles. A - It is required for long-chain fatty acid oxidation. B - It helps to withdraw groups of excessive acyl in the mitochondria. C - It plays an important role in detoxification of the body. Skeletal muscles are dependent on optimal performance of metabolic processes during exercise. Researches on the effects of carnitine supplementation on exercise performance indices are more or less divergent and heterogeneous. The upshot of these findings, however, indicates the beneficial effects of carnitine. In a general review by Heidrum *et al.,* (2004) the positive effects of L-carnitine on exercise performance were reported in 14 studies comprising 305

subjects, and only in 7 studies on 70 people no beneficial effects (without the harmful side effects) were identified. Another study on 110 athletes confirmed the athletic performance enhancement effect following carnitine loading (Robert *et al.,* 1998). In Colombani's *et al.,* (1996) research seven marathon runners consumed 2 g L-carnitine before and again 2 g after 20 kilometers running and continued the marathon to the end. Despite a significant increase in plasma carnitine no significant change was observed in running time, respiratory exchange ratio, carbohydrate plasma concentration (glucose, lactate, pyruvate) and fat metabolites (free fatty acid, beta-hydroxybutyrate, glycerol), insulin, glucagon, cortisol hormones and enzyme activities (creatine kinase, lactate dehydrogenase) and recovery phase . Also Trappe's study (1994), reported no energizing benefit of L-carnitine during anaerobic interval swimming in skilled swimmers (Trappe *et al.,* 1994). In another study, the daily consumption of 2 g carnitine by elite runners, led to 5.7% increase in running speed and in untrained individuals it brought about endurance performance to some extent similar to that of athletes (Robert *et al.,* 1998). Oral carnitine supplementation caused a small decrease in heart rate of exercise with the intensity of 50% VO_{2max} which suggests the improvement of circulatory system during sub-maximal exercise (Natali, 1993). Also, a daily supplementation of 5 g L-carnitine for five days led to a 5 to 7 percent decline in heart rate during cycling exercise (Soop *et al.,* 1998). The inconsistencies in research findings can be ascribed to individual differences and the differences in methodology and sport protocols. On the other hand, some scientific sources suggest that L-carnitine supplementation stimulates muscle metabolism even if not associated with changes in the muscle concentration (Sherman *et al.,* 1981). Researchers believe that L-carnitine is able to decrease amplified plasma glucose concentration compared to no supplementation conditions. It seems that this effect is not associated with insulin-dependent mechanism (Soop *et al.,* 1998). L-carnitine is effective in enhancing peripheral blood products and capillary dilation and boosts the intake of oxygen and other nutrients, especially during exercise (Sherman *et al.,* 1981). Supplementation of L-carnitine stimulates haematopoiesis capacity when living in elevated areas or in hypoxia conditions (Matsomoto *et al.,* 2001).

The burning process fatty acids have a direct relationship with the ability to decrease total cholesterol and LDL cholesterol (bad cholesterol) and simultaneously with the increase of HDL cholesterol (Good cholesterol). Carnitine's role in reducing artery stenosis, particularly coronary injuries and the risk of vascular occlusion has been demonstrated (Horleys, 2003). In one study, after 4 months of carnitine therapy, the levels of total cholesterol and triglyceride decrease respectively 20 and 28% and HDL Cholesterol concentration increased by 12% (Arsenian *et al.,* 1997). In response to carnitine supplementation, triglyceride and HDL cholesterol are more sensitive (16).

Because carnitine plays an essential role in lipid metabolism, this substance is a major nutrition in weight loss besides physical activity and appropriate diet. In a study on weight loss of 13 to 17 year-old students, the subjects were divided into two experimental and placebo groups with identical diet and physical activity, with the exception that the experimental group used 2 grams of L-carnitine on a daily basis. After completion of the research there was a 1.5 pound weight loss in the placebo group, but in the experimental group there was a weight loss of 11 pounds (Soop *et al.,* 1998).

L-carnitine Supplementation and fatty acid oxidation

Fatty acid is an important source of energy for muscles at rest and in prolonged exercise with moderate intensity. Aerobic exercise increases fat oxidation capacity in the skeletal muscle (Holloszy *et al.,* 1970). A 12-week aerobic exercise including running 2 hours a day on treadmill, doubled carnitine the activity palmitoyltransferase enzyme (Twin muscle). Carnitine has a key role in lipid metabolism by transporting long-chain fatty acids into mitochondria for energy production (Soop *et al.,* 1998).

Carnitine supplementation stimulates fat oxidation during exercise and glycogen storage and delays the outset of fatigue. However, increased demand for fatty acid oxidation during exercise depends on normal levels of body carnitine. The results of studies in this field are heterogeneous. In a study on mice by changes in dietary intake of carnitine, the first, second and third groups respectively experienced a 50-percent decrease; a 50% increase and no change in Carnitine intake for the same period of time. At the

end, the findings showed that during exercise test, palmitic acid oxidation and exercise capacity were equal in all three groups (Eizadi[a] *et al.,* 2011). Nevertheless, many researches have reported the beneficial effects of L-carnitine on lipid metabolism. The positive role of L-carnitine loading on lipid metabolism in patients with carnitine deficiency is quite obvious. For the first time ever, a study reported with the full confidence the carnitine supplementation advantages in increasing long-chain fatty acid oxidation in people without carnitine deficiency (Brass 2000). Also Dragan et al gave swimmers L-carnitine injections (1g) and observed significant positive effects on the intake of fatty acid triglyceride and lactate. On the other hand, in another study it was found that compared with carbohydrate, carnitine supplementation significantly increases fat oxidation in the recovery period after intense aerobic exercise (Natali, 1993). In a study of L-carnitine supplementation, reduced the respiratory quotient from 0.9 0.88 which is suggestive of increased fat oxidation against carbohydrate (Natali, 1993). Additionally, L-carnitine supplementation (3g) plus heparin injection led to significant decrease in serum triglyceride during a submaximal cycling exercise (Huertas *et al.,* 1992).

Daily intake of 2 g L-carnitine by 14 endurance runners for one month led to a significant increase in cytochrome reductase, succinate cytochrome reductase and cytochrome oxidase mitochondrial enzymes. The results reveal that L-carnitine supplementation increases respiratory chain enzymes activity probably due to prompting certain mechanisms in mitochondrial DNA (Eizadi[b] *et al.,* 2011). But, in a recent study, no differences in FFA concentrations were observed during exercise after carnitine supplementation compared to their respective baseline values (Joaquin *et al.,* 1998).

L-carnitine Supplementation and carbohydrate metabolism

Although the main role of carnitine is in lipid metabolism, scientific evidence confirms its role in the metabolism of carbohydrate. In fact, there is a strong correlation between muscle carnitine and Krebs cycle; muscle carnitine concentration is directly proportional to muscle glycogen reserves. Also due to its muscle glycogen storage effect, carnitine acts as a glycogen anti-catabolic agent which effectively reduces the need to burn glycogen (Horleys, 20033).

L-carnitine Supplementation and Branched amino acid metabolism

Carnitine levels are associated with metabolism of branched amino acids that are the most important amino acids in exercise performances (Horleys, 2003). Carnitine stimulates amino acid decarboxylase by increasing conversion of branched keto-analogues to carnitine esters (Brass, 2000). Carnitine - Branched amino acid complex is of particular importance in the liver in order to increase energy production due to hepatic gluconeogenesis (Horleys, 2003).

Carnitine and activity of Pyruvate dehydrogenase complex

Scientific studies indicated that in addition to increasing fat oxidation carnitine supplementation leads to increased oxidation of glucose into lactate which brings about further ATP production (Brass 2000). In the study of Arnaz et al 6-month supplementation of L-carnitine on athletes led to increased activity of pyruvate dehydrogenase enzyme (Brass, 2000). Also the daily intake of 2 g L-carnitine for 4 weeks significantly increased the activity of Pyruvate dehydrogenase during exercise (Barnett *et al.,* 1998). Increased activity of pyruvate dehydrogenase subsequent to carnitine supplementation has also been mentioned in some other studies (Natali, 1993; Eizadi[a] *et al.,* 2011).

Carnitine and Lactate Accumulation

Intense or increasing activity leads to accumulation of lactate accompanied by reduced serum PH levels. High levels of lactic acid increase acidity of blood and tissues which causes fatigue and decreased ATP production. L-carnitine is an inhibitor of the key anaerobic enzyme, Phosphofructokinase (PFK) and slows down glycolysis. An Italian researcher in 1990 cited that carnitine supplementation reduces plasma lactic acid accumulation during exercise (Horleys, 2003). L-carnitine decreases the ratio of acetyl-CoA to CoA and this factor stimulates the activity of pyruvate dehydrogenase. It is commonly held that after carnitine supplementation, one the one hand conversion of pyruvate to acyl CoA increases due to increased pyruvate dehydrogenase and brings about further acetyl carnitine synthesis. On the other hand, the activity of lactate dehydrogenase, which reverts pyruvate to lactate, decreases and this in turn, would

decrease lactic acid accumulation during maximal and exhausting exercise (Eizadi[a] *et al.,* 2011). Alternatively in Barnett's study, the consumption of L-carnitine caused no significant change in blood lactate levels during short-term maximal exercise (Barnett *et al.,* 1998). Also, No significant change in Lactate accumulation was observed immediately and exercise test by 3g L-carnitine supplementation (Sohaily *et al.,* 2011).

But in another study, consumption of 2 g L-carnitine just one hour before exhausting cycling exercise, led to a significant reduction in accumulation of lactic acid (Vecchiet *et al.,* 1991). Other studies too have reported beneficial effect of L-carnitine loading on the reduction of lactate accumulation (Natali 1993).

L-carnitine and Immunity System:

During cellular respiration in strenuous exercise, oxygen variations, which have been partially reduced and are extremely reactive with proteins, lipids and DNA, called free radicals, are created.

In this regard Davis et al., (1982) have reported that following the exercise performance by rats to the border of exceeding fatigue, the density of free radicals in liver and muscle increases two to three times. The most destructive effects of free radicals is directed at mitochondrial DNA which can bring about mortality and incidence of lung, skin, stomach and prostate cancers and also causes the activation of inactive enzymes and destruction of other cellular parts by damaging mitochondria lysosomes and walls (Joaquin *et al.,* 1998). Carnitine prevents cell damage induced by free radicals and the more the cell contains carnitine, the later cellular death will occur. More recent studies have shown that carnitine and especially acetyl-carnitine play an extraordinary role in protecting the body and the mitochondria from free radicals. It also reinforces the immune system with age and adulthood (Horleys *et al.,* 2003, Brooks *et al.,* 1998).

Ammonia is a result of protein degradation and is effective in onset of fatigue during exercise. Carnitine supplementation decreases ammonia accumulation during exercise, in particular under hypoxic conditions through activation of urea cycle and reduction of free radicals (Horleys, 2003). Also L-carnitine protects against neurotoxicity resulting from high levels of ammonia (Natali, 1993). Wolek and Kramer reported that carnitine decreases purine catabolism, formation of free radicals and destruction of Sarcolemma in delayed fatigue period (Natali, 1993).

Carnitine and Maximal Oxygen Consumption (VO_{2max})

Many studies have been conducted on the impact of carnitine loading on maximum oxygen consumption (VO_{2max}) in athletes and non athletes. Most of these research more or less report improved VO_{2max} and performance in elite and non-professional athletes after L-carnitine supplementation, especially after longer term intake of high doses (Sherman *et al.,* 1981, Barnett *et al.,* 1998). However, some preliminary researches have denied increased VO2max in healthy athletes due to carnitine supplementation. In patients with respiratory inefficiency, carnitine supplementation has been observed to impact the increase of VO_{2max} and less lactate production and more rapid recovery (Natali, 1993). The daily intake of 2 g carnitine significantly increased maximum oxygen consumption and decreased pulmonary ventilation, lactate and C_{O2} production (Sherman *et al.,* 1981). In another study, L-carnitine supplementation (3g) plus heparin injection led to significant decrease in VO2max during a submaximal cycling exercise (Huertas *et al.,* 1992).

Carnitine supplementation and its concentrations during exercise

Tissue concentrations of carnitine in athletes and ordinary people have been reported to be identical. The combined effects of exercise and diet on muscle carnitine levels have been almost relatively measured. Carnitine intake depending on the mode of intake, dosage and duration of use, potentially causes a change in concentration and its pharmacologic advantage. Maximum absorption of L-carnitine in plasma takes place 3 to 5 hours after the supplementation. Holtman et al have emphasized that a supplementation program of several days or several weeks, does not change the muscle total carnitine. The available findings also confirm that the amount of muscle carnitine does not increase tangibly by such types of supplementation, while plasma carnitine concentration increases. The intake of less than one mole of

carnitine increases plasma carnitine concentration without changing muscle carnitine. Although muscle concentration of carnitine remains unchanged its supplementation continues to affect indicators of exercise physiology and performance. Of course is possible to increase muscle carnitine level by long-term supplementation (Brass, 2000).

In resting condition, out of the entire carnitine available in the muscle approximately 80% is in form of total L-carnitine and 20% is in form of acetyl carnitine with short and long chain. Performing light and moderate exercise (below lactate threshold) does not cause significant changes in muscle carnitine levels. But with 10 minutes of intense exercise, muscle total carnitine would be replaced by short chain acetyl-carnitine so that only 20 to 50 percent of the entire carnitine would be available in form of total L-carnitine and 45 to 70 percent of the entire carnitine would be available in form of short chain acetyl carnitine (Sherman *et al.,* 1981). It has been reported in early studies that the entire muscle carnitine decreases by 20% during 40 minutes of exercise at 55%VO_{2max} intensity. Soop et al skillfully calculated the arterial-venous difference of carnitine in the shins of active individuals as well as uptake and release of muscle carnitine. The results showed that during physical activity a slight decrease occurs in muscle carnitine and there is a stronger tendency to absorb acyl carnitine. In another study by Soop it was found that decreased carnitine reported in his previous studies, had been overstated. The results are consistent with some recent findings that have not observed a significant decrease in total carnitine and its esters. Acetyl carnitine accumulation occurs in proportion with exercise intensity. Exercise at intensities of lower than 30%VO_{2max}, usually does not prompt formation of acetyl carnitine. But during intense exercise, free carnitine concentration decreases from 77-90 percent in resting position to 30-37 percent. This decrease is compensated by concurrent increase of acetyl-carnitine. This means that during increasingly intense and exhausting exercise, the decrease of concentration of free carnitine is approximately proportional to the increase of acetyl carnitine concentration (Eizadi[a] *et al.,* 2011). Sampling of Vastus Latralis muscle before and after an exhaustive cycling exercise revealed that acetyl-carnitine concentrations in the type I fibers (slow contraction) is more then that of type II (fast contraction) is. Also, acetyl carnitine accumulation in type I fibers is higher during exercise, but the concentration of free carnitine at the end of the exercise was significantly lower in these fibers than in type II fibers. However, the sum of free carnitine and acetyl carnitine remained unchanged before and after exercise. The higher carnitine accumulation in type I fibers acetyl during prolonged exercise, is probably because of the higher carnitine capacity of this type of fibers (Constantin *et al.,* 1996). Previous studies indicate that any change in carnitine metabolism during exercise is dependent on the intensity and work load which is indicative of the impact of L-carnitine under increasingly intense prolonged exercise. Decombaz *et al.,* (1992) concluded that in athletes with moderate carnitine diet moderate exercise would not lead to a decrease in muscle carnitine.

In general, muscle total carnitine does not change during intense or endurance exercise and the reduction of skeletal muscle carnitine in healthy individuals after any level of exercise intensity is quite unlikely (Eizadi[a] *et al.,* 2011; Decombaz *et al.,* 1992; Wachter *et al.,* 2002; Carlin *et al.,* 1986). In contrast, plasma carnitine level increases significantly during exercise. Increased plasma esterified carnitine is due to depletion of muscle free carnitine. Researches in this area indicate that plasma concentrations of free carnitine increases after short-or long-term exercise (Decombaz *et al.,* 1992; Carlin *et al.,* 1986; Oyono *et al.,* 1998).

Permissible pharmaceutical does and carnitine supplementation safety

Carnitine enters the body both through the diet and it is also synthesized endogenously in the body so it is rather difficult to determine its intake doses in normal conditions or under different disease as well as different ages. The daily intake of one to two grams of carnitine during intense exercise periods is common among athletes. 1 to 2 gram capsules should be taken 30 minutes before exercise. It is better to do the supplementation in the mornings and evenings. Those who use carnitine supplementation to improve athletic performance should stop using carnitine for one week every month. In non-athletic conditions L-carnitine is recommended to be taken with food. Capsules, tablets or powders are to be taken mixed with foods or fluids (Horleys, 2003). No important side effects following oral or pharmaceutical

supplementation of L-carnitine in humans or experimental animals or mortality risk have been reported even when high doses of these supplements have been administered (Maher , 2001). In studies in which L-carnitine supplementation reached even more than 15 grams per day, the results emphasized high tolerance in individuals only a slight stomach complaints or diarrhea was observed. On the other hand, no physical and psychological dependence or addiction has been observed even after long-term use (Maher , 2001; Horleys *et al.,* 2003).

CONCLUSION

Many studies on the impact of carnitine supplementation on exercise performance in athletes and ordinary people have been conducted and their results are more or less contradictory. The role of carnitine and its substrates in transport of long chain fatty acids into the mitochondria and increasing their oxidation is well proven. Some researchers believe that in healthy individuals the internal synthesis and daily uptake of carnitine from the diet is adequate to satisfy energy production requirements, but the potential role of its loading is well marked in individuals suffering some kind of carnitine deficiency. Although there is little information about it, there is minimum acceptable scientific evidence at hand that support L-carnitine as a useful factor in aerobic and increasing performance. In a general review of the research history it can be concluded that L-carnitine as an energizing and sugar anti-catabolic factor starts to act during exercise performance of athletes and its supplementation has advantages like increased oxidation of fatty acid, increased glycogen storage, decreased lactic acid concentration, capillary dilation and transmission of blood byproducts, increased metabolism of branched amino acids and ammonia removal and protection of the immune system. Prolonged athletic performance reduced respiratory efficiency, increased maximum oxygen consumption, and delay in the fatigue, are also other possible effects of L-carnitine supplementation that have been mentioned in most studies.

REFERENCES

Arsenian MA. 1997. Carnitine and its derivatives in cardiovascular disease. *Progress in Cardiovascular Diseases* 40(3):265-86.

Barnett C, Costil DL, Vukovich MD, Cole KJ, G oodpaster BH, Trappe SW et al. 1998. Effect of L-carnitine supplementation on muscle and blood carnitine muscle content and lactate accumulation during high-intensity sprint cycling. *International Journal of Sport Nutrition* 4(3):280-8.

Brass EP. 2000. Supplemental carnitine and exercise. *The American Journal of clinical nutrition* 72(2): 6185-6235.

Brooks Jo 3d, Yesavage JA, Carta A, Bravi D. 1998. Acetyl-L-carnitine slowws decline in younger patients with Alzhemers disease: A reanalesis of a double-blind, placebo-controlled trail using the trilliner approach. *International Psychogeriatrics* 10(2): 193-203.

Carlin II, Redan WG, Sanjak M, Hodach R. 1986. Carnitine metabolism during prilonged exercise and recovery in humans. *Journal of Applied Physiology* 61(4): 1275-8.

Colombani P, Wenk C, Kunz I, Krahenbuhl S, Kuhnt M, Arnold M. 1996. Effects of L-carnitine supplementation on physical performance and energy metabolism of endurance-trained athletes: a double-blind crossover field study. *E uropean Journal of Applied physiology and Occupational physiology* 73(5) 434-439.

Constantin-Teodosiu D, Howell S, Greenhaff PL. 1996 Mar. Carnitine metabolism in human muscle fiber types during submaximal dynamic exercise. *Journal of Applied Physiology* 80(3): 1061-4.

Davies RL, Weintaub AB.1987. Expresion of a single transfected cDNA converts fibroblasts to myoblasts. *Cell* 51(6): 987-1000.

Decombaz J, Gmuender B, Sierro G, Cerretelli P. 1992. Muscle carnitine after strenuous endurance exercise. *Journal of Applied Physiology* 72(2): 423-7.

Eizadi M, Behbudi L, Shafiei M, Afsharmand Z (2011). Fat metabolism and aerobic capacity does not affect by acute L-carnitine L-tartrate supplementation. *Journal of Applied Environmental and Biological Sciences* 1(12): 695-699.
Eizadi M, Khorshidi D, Samarikhalaj H, Dooaly H (2011). Effects of Increased FFA Availability on Aerobic Capacity During Cycling Exercise. *Journal of Applied Environmental and Biological Sciences* 1(10): 482-488.
Francis B, Stephens D, Constantin T, Paul L (2007). New insights concerning the role of carnitine in the regulation of fuel metabolism in skeletal muscle. *Journal of Physiology* 581(2): 431–444.
Fredric M, VA and Ronald J. A. Wanders. 2002. Canitine biosynthesis in mamals. Univercity of Amsterdam. *Biochemical Journal* 361(3): 417-29.
Heidrum K, Alfred L. 2004. Supplementation of L- carnitine in athletes: does it make sense. *Nutrition journal* 20(7 – 8): 709-715.
Holloszy JO, Oscai IJ. 1970. Mitochondrial citric acid cycle and related enzymes, adaptive response to exercise. *Biochemical and Biophysical Research Communications* 40(6): 1368-73.
Horleys. 2003. L-Carnitine. A division of Naturalac Nutrition. Level 2. Available from: http:// horleys. com.
Huertas R, Campos Y, Diaz E, Esteban J, Vechietti L, Montanari G et al. 1992. Respiratory chain enzymes in muscle of endurance athletes: effect of L-carnitine. *Biomechanical and biophysical research communications* 188(1): 102-107.
Joaquin A, Juan C, Rubio MA, Martin, Yolanda Campos. 1998. Biological roles of L-carnitine in perinatal metabolism. *Early Human Development* 53 (Supplemental): 43-50.
Joaquin A, Rose H, Yolanda CA, Enrico D, Jose MV, Esther V. 1994. Effects of of L-carnitine of the pyruvate dehydrogenase complex and carnitine palmytoyl transferase activites in muscle of endurance athletes. *FEBS Letters* 341(1): 91-93.
Li B, Lioyd ML, Gudjonsson H, Shug AL, Olsen WA. (1992). The effect of enternal carnitine adminestration in humans. *The American journal of clinical nutrition* 55(4): 838-45.
Matsomoto YI, Amano S. 2001. Effects of L-carnitine supplemenation of renal anemia in poor responders to erythropoietin. *blood purification* 19(1): 24-32.
Natali A. 1993. Effects of acute hypercarnetinemia during increased fatty substrate oxidation in man. *Metabolism* 42(5): 594-600.
Oyono-Enguelle S, Freund H, Ott C, Gartner M, Heitz A, Marbach J. Prolonged submaximal exercise and L-carnitine in human. *European journal of applied physiology and occupational physiology* 58(1-2): 53-61.
Robert C. 1998. Carnitine may benefit Athletes. *Journal of theAmerican College of Nutrition* 17(6): 646-650.
Sherman WM, Costill DL, Fink WJ, Miller JM. 1981. The effect of exercise and diet anipulation on muscle glycogen and its subsequent use during performance. *International Journal of sport Medicine* 2(2): 114-118.
Sohaily S, Eizadi M, Faraji G, Kamyabnya M (2011). Aerobic Capacity and Glucose Metabolism in Response to Oral Carnitine Ingestion in Healthy People. *Journal of Basic and Applied Scientific Research* 1(9): 1305-1309.
Soop M, Bjorkman O, Cederblad G, Hagbenfeldt L, Wahren J. 1998. Influence of carnitine supplementation on muscle subestrate and carnitine metabolism during exercise. *Journal of Applied Physiology* 64(6): 2394-9.
Maher T (2001). L-carnitine. In: l-carnitine continuing education module. Massachuesetts: Macher 38(1): 1-8.
Trappe SW, Costill DL, Goopaster B, Vukovich MD, Fink WJ. 1994. The effects of L-carnitine supplementation on performance during interval swimming. *International Journal of sport Medicine* 15(4): 181-5.

Vecchiet L, Dilisa F, Pierlisi G, Ripari P, Menabo R, Giamberardino MA, Siliprandi N. 1991. Influence of L-carnitine adminstration on maximal physical exercise. *European journal of applied physiology and occupational physiology* 61(5-6): 486-90.
Wachter S, Vogtm M, Kreis R, Boesch C, Bigler P, Hoppeler H, Kerahenbuh S. 2002. Long-term adminstration of L-carnitine to human: effect on skeletal muscle carnitine content and physical performance. *Clin chim Acta* 318(1-2): 51-61.