L-Carnitine And The Heart

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Summary:

Cardiac Ischaemia may be defined as a deficiency in cardiac energy supply relative to energy demand. In coronary artery disease (CAD), Oxygen supply is limited due to coronary obstruction so energy production is not enough to meet the energy demands for work. Several reports involving about 2500 patients of CAD where carnitine was administered for upto 1 year show some beneficial effects. There is reduction in ischaemia showing reduced ST-segment depression and angina, greater effort tolerance and decreased need of cardiac drugs, Carnitine can cause overall improvement in cardiac performance in patients with CAD as well as in cardiomyopathy. More studies are necessary to demonstrate whether carnitine can scavenge free radicals apart from its beneficial effect on fatty acid metabolism. Side effects of carnitine are mild nausea and vomiting and doses upto 2g/day in 3 divided doses may not have any side effects. Intravenous L-carnitine acts rapidly and has no side effects.

Introduction:

Levo-carnitine (L-carnitine) is a naturally occurring nontaxic substance which is considered neither a vitamin nor an essential nutrient[1,2]. It is a necessary cofactor for fatty acid oxidation and energy production[1-3]. Exogenous sources of L-carnitine are: red meat, milk and milk products.[1] Endogenously, it is synthesized in the liver and kidneys from amino acids; lysine, and methionine and is a quarternery amine[1,2]. Of the total carnitine content present in our body, 97.8% is found in cardiac and skeletal muscles, 1.6% in liver and 0.6% in plasma[1,2]. Of the total plasma carnitine, 75% is free carnitine and 25% is esterified carnitine (Acyl-carnitine) which may have adverse effect if it is higher.[1]

Carnitine deficiency:

Carnitine deficieny can occur due to poor dietary intake and due to defective metabolism (Table 1). Carnitine deficiency influences the functional capacity of the cell. It decreases the availability of energy for various functions of the cells. There is pathological accumulation of fatty acids in the cytoplasm due to carnitine deficiency which are highly toxic to cell membranes and structure[1,3]. Carnitine levels are lower in vegetarians compared to nonvegetarians.

Normal plasma levels of carnitine are 50 umol/L for men and 40 umol/L for women and the levels were slightly higher in obese subjects[1,4]. The biosynthesis of carnitine occurs in liver and kidneys, therefore any chronic renal or liver disease may also cause carnitine deficiency which may be marked if the intake of dietary carnitine is also lower. Table 2 shows the list of diseases which may be associated with carnitine deficiency. Carnitine deficiency may be either primary or secondary. In primary deficiency, low concentration of carnitine in the blood and tissues occur because of impaired biosynthesis or transport of carnitine in the body whereas in secondary deficiency, low concentration of carnitine in the blood and tissue occur due to genetic or acquired diseases,[1-3] or primary carnitine deficiency may be myopathic in which serum carnitine may be normal but carnitine may be depressed in the muscle.

Metabolic role of L-carnitine:

It performs 4 important functions which appear to be important for life or death of the cell[1,5]. It is essential for the transfer of long chain fatty acids from the

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cytoplasm in to the mitochondria, permitting beta-oxidation and producing energy in the form of ATP. L-carnitine encourages the oxidative utilisation of glucose preventing excessive formation of lactic acid via anaerobic pathway which can damage skeletal muscles and myocardial cells. It prevents the inhibition of Adenine nucleotide translocase an enzyme responsible for passage of ADP from the cytoplasm into the mitochondria, and passage of energy rich ATP from the mitochondria into the cytoplasm. These properties of L-carnitine increase the availability of ATP at the site of utilisation. L-carnitine can also inhibit the overproduction of free radicals which are damaging to cell[6,7].

L-carnitine in coronary artery disease:

There is evidence that free L-carnitine concentrations in the myocardial tissue from the infarcted area was much lower than from noninfarcted area in victims dying of acute myocardial infarction (AMI).[8] Intermediate levels of L-carnitine in the infarct border zones and equal levels in the healthy myocardium and heart surgery patients[9] indicated that L-carnitine may have a role in myocardial ischaemia. In myocardial ischaemia or hypoxia, there is a rapid inhibition of oxidative processes and a reduction in tissue levels of free L-carnitine which results into increased free fatty acids in the cytoplasm of myocardial cells leading to necrosis.[1,3] In acute experimental myocardial ischaemia, there is progressive reduction in total L-carnitine which is proportional to the extent and duration of myocardial ischaemia. These findings suggest that the maintenance of the physiological levels of L-carnitine and the ratio of acetylcarnitine/free carnitine may be important in the regulation of myocardial metabolism during injury to myocardium. Hypocarnitinemia and hypocarnitinecytia have also been observed in patients with angina pectoris, myocardial infarction and heart failure. It is possible that treatment with carnitine may be protective in patients with coronary artery disease (CAD).[7,9] However, accumulation of long chain acylcarnitine during ischaemia may have adverse effects.

Table 1
Mechanisms of Carnitine Deficiency

1.	Lower intake of dietary carnitine
2.	Defective intestinal absorption
3.	Excessive renal loss
4.	Defective biosynthesis of carnitine in diseases of the kidney or liver
5.	Higher acyl conjugation
6.	Defective intracellular transport affecting uptake or release of carnitine

Carnitine administration may cause decreased production of lactate in the myocardium or improve extraction during sinus pacing or at rest compared to untreated or placebo group[5]. Prior treatment with L-carnitine in coronary artery bypass surgery among 40 patients caused decreased concentrations of lactate in the myocardium which correlated with significantly higher levels of ATP[9]. In one study, the effect of orally administered L-carnitine, 40mg/kg daily was studied on cardiac enzyme (CPK-MB) in 22 patients of AMI during a followup of 48-72 hours. Treatment with L-carnitine was associated with a decreased release of CPK-MB (465 vs 520 mg/L) in the intervention group compared to control subjects[10].

In a randomized, double blind placebo controlled trial[7], the effects of the administration of oral L-carnitine (2g/day) for 28 days were compared in the management of 51 patients (carnitine group) and 50 (placebo group) patients with suspected acute myocardial infarction. At study entry, the extent of cardiac disease, cardiac enzymes and lipid peroxides were comparable between the groups, although both groups showed an increase in cardiac enzymes and lipid peroxides. After 28 days treatment period, the mean infarct size assessed by cardiac enzymes showed a significant reduction in the carnitine group compared to placebo. Electrocardiographic assessment of infarct size revealed that the QRS-score was significantly less in the carnitine group compared to placebo while serum aspartate transeminase and lipid peroxides showed significant reduction in the carnitine group. Lactate dehydrogenase measured on the sixth or seventh day following AMI showed a smaller rise in the carnitine group compared to placebo. The primary substrates for the formation of lipid peroxides are fatty acids and long chain acyl coenzyme A. derivatives whose concentration increase during AMI. It is possible that carnitine increases the transport of fatty acids and inhibits free radicals and lipid peroxides by decreasing the availability of fatty acids.

TABLE 2

Causes of Carnitine Deficiency

Primary deficiency	Secondary deficiency
1. Cardiomyopathy	1. Myocardial infarction
2. Muscular dystrophy	2. Angina pectoris
3. Hereditary disorder affecting fatty acid metabolism	3. Heart failure
	4. Anticancer drug therapy
	5. Valproate induced toxicity
4. Acute neonatal crisis	6. Organic acidurias
5. Ageing	7. Total parenteral nutrition
	8. Hemodialysis
	9. Kidney and liver diseases due to decreased synthesis

In one study[11] involving 146 patients of AMI (97 control and 49 treatment group), treatment with L-carnitine (9g/day IV, 3 days initially) in a dose of 4g/day for 21 days showed no death in the treatment group compared to 18 deaths in the control group. In a controlled multicentre study[12] 200 patients with angina pectoris, 100 randomly selected patients were administered L-carnitine (2g/day) for a follow-up period of 6 months. There was a significant decrease in ventricular premature beats at rest, increased tolerance to exercise in terms of increased maximal cardiac frequency, increased maximal systolic arterial blood pressure, and therefore increased double cardiac product and reduced ST-segment depression during maximal effort. Davini et al[13] studied the effect of L-carnitine (4g/day) in 81 randomly selected patients of recent AMI and compared with 79 control subjects for 1 year. Treatment with carnitine showed significant reduction in heart rate, angina pectoris and deaths (1.2 vs 12.5%, $p<0.005$) in the intervention group compared to control group.

On the basis of Italian research, an open study[14] was conducted with L-carnitine (2g/day) among 148 patients of angina pectoris. Treatment was continued for a follow-up period of 6 months. The results were compared to the same studies conducted in Italy and Germany. There was a substantial reduction in episodes of angina and nitroglycerine consumption in treated patients compared to others not given this drug. The evaluation of the quality of life assessed by questionnaire showed significant benefit with L-carnitine. In one analysis[15], 3525 patients with cardiac disease were administered 2g/day of L-carnitine for 1 year. Of these 3525 patients, 220 had stable angina and 59 had angina with congestive heart failure. These patients were compared with 148 patients from Switzerland and 143 patients from Germany receiving treatment for 6 and 3 months respectively. Analysis of the 3 trials showed net reduction in episodes of angina, reduction in nitrate consumption, improvement in physical performance and quality of life in the carnitine groups compared to other patients. In the Indian experiment, treatment with L-carnitine showed less nonfatal infarction and deaths in the intervention group compared to control group[7].

In a recent study[16] involving 472 patients with a first acute myocardial infarction, treatment with L-carnitine was associated with a significant attenuation of left ventricular dilation in the first year after treatment compared to placebo group. The per cent increase in both end-diastolic and end systolic volumes from admission to 3,6 and 12 months evaluation was significantly reduced in the L-carnitine group. No significant differences were observed in the ijection fraction changes over time in the two groups. Although not designed to demonstrate differences in clinical end points,

TABLE 3

Effect of L-carnitine on complications of Acute Myocardial Infarction

	Carnitine	Placebo	Relative Risk (95% C.I.)
	n (%)		
Angina pectoris	9(17.6)	18(36.0)	0.49 (0.24-0.98)
NYHA Class III and IV heart failure	4(7.8)	7(14.0)	0.56 (0.17-1.86)
Total cases with poor left ventricular function	12(23.4)	18(36.0)	0.65 (0.35-1.24)
Total arrhythmias	7(13.7)	14(28.0)	0.49 (0.21-1.41)
Hypotension	1(1.9)	3(6.0)	0.31 (0.03-2.79)

the combined incidence of death and congestive heart failure after discharge was 14(6%) in the L-carnitine group versus 23 (9.6%) in the placebo group (P=NS). Incidence of ischaemic events during the follow-up was similar. Since left ventricular dilation after AMI, in particular end systolic volume represents the most powerful prognostic indicator for clinical events, it is possible that treatment with L-carnitine early after AMI can decrease cardiac events.

A couple of small studies have examined the effect of carnitine on the response to atrial pacing-induced tachycardia in patients with CAD[17]. Ferrari and coworkers[5] noted a reduction in left ventricular end diastolic pressure after intravenous infusion of L-carnitine in patients with CAD (Table 4). In a study by Reforzo and coworkers[17], carnitine diminished the magnitude of ischaemic-type ST-segment depression that occurred during tachycardia stress. In both studies, carnitine caused a significant increase in myocardial lactate extraction during tachycardia stress. Canale et al and Cherchi et al showed that treatment with carnitine was associated with improvement in exercise capacity and electrocardiographic manifestations of ischaemia[17]. Maximal workload increased and the degree of ST-segment depression at Maximal workload declined. Echocardiographic evaluation in some of these studies showed improvement in left ventricular function[17].

Carnitine administration has also been reported to provide benefit in congestive heart failure, arrhythmias, anthracycline induced cardiotoxicity, peripheral vascular disease and myocardial damage due to any other cause which need more studies[1-3].

Mechanism:

The exact mechanism of action, how carnitine modulates myocardial metabolism is poorly known. In acute MI, it is possible that L-carnitine inhibits the 4 major consequences of lipid accumulation in the myocardial cells[1-3, 17].

1. Reduced ATP production due to inefficient utilisation of free fatty acids causing reduced ATP generation.
2. Increased lactate production due to the inhibition of oxidative utilisation of glucose causing increased lactic acidosis.
3. Inhibition of Adenine Nucleotide Translocase (ANT), the enzyme responsible to make ATP available to the myocardium causing decreased activity of ANT.
4. Overproduction of free radicals due to lipid oxidation and ischaemia causing increased free radical and lipid peroxides which are toxic to cells.

Thus lipid accumulation reduces the over-all cardiac performance due to lower ATP generation, lactic acidosis, lower, ANT enzyme and free radical generation[7]. Reduction in over-all cardiac performance is manifested as[17]:

1. Left ventricular dysfunction.
2. Increase in ischaemia and angina.
3. Negative ionotropic effect.
4. Arrhythmias.
5. Deterioration of the NYHA class.
6. Hypotension and shock.

The over-all cardiac performance can be improved by extending a metabolic support to the myocardium by treatment with L-carnitine[1-3,7]. L-carnitine transfers the fatty acids for energy production, encourages oxidative utilisation of glucose, prevents the inhibition of Adenine Nucleotide Translocase (ANT), removes the toxic fatty acid metabolites and inhibits free radical generation[1-3,7]. These beneficial effects on myocardial metabolism due to carnitine therapy may cause increased generation of ATP, reduce lactic acidosis, increase the availability of ATP to myocardium and decrease the free radical induced cardiac damage[7,17]. These influences of L-carnitine may provide over-all cardioprotective effect which manifest as reduction in arrhythmias, angina and ischaemia, improvement in left ventricular function and improvement in overall cardiac performance.

Dyslipidemia:

Since L-carnitine is necessary for the transport and metabolism of fatty acids in tissues, it is possible that its deficiency may contribute to hypertriglyceridemia and low high density lipoprotein cholesterol (HDL). In

uraemia patients with hypocarnitinemia and hypertriglyceridemia, treatment with carnitine was associated with significant reduction in serum triglycerides after 1 to 8 months[1,18]. The increase in HDL cholesterol may be more marked in subjects whose levels are <40mg/dl. A few reports showed a rise in triglycerides on treatment with carnitine indicating that more studies are necessary. It is possible that carnitine deficiency may be a risk factors of hypertriglyceridemia and low HDL and carnitine supplementation may reverse alcohol induced fatty liver and hypertriglyceridemia[18,19]

Cardiomyopathy:

Cardiomyopathy is the predominant feature of the systemic carnitine deficiency in which both serum and tissue levels of carnitine are abnormally low and multisystem involvement is common. Encephalopathy,

Table 4

Effect of L-carnitine in ischaemic heart disease

Author	n	Duration	Dose	Cardiac function	Stress testing	Electo-cardiographic changes	Clinical outcome
Ferrari (1984)	11	<30days	IV 40mg/kg IV	LVEDP lactate extraction	tachycardia tolerance		
Kosolcharoen (1981)	19	-	-	Reduced HR and RPP	time to angina	ST depression	Improved Clinical status
Sciveres (1984)	40	15days	Oral 2g/day	-	-	-	Nitrate use
Cherchi (1985)	44	28days -	Oral 2g/day	-	-	-	Angina
Reforzo (1986)	19	<30days	40mg/kg	lactate	-	-	
Canale (1988)	16	28days	Oral	Improved LV function	workload	-	Angina
Cherchi (1990)	18	28days	1.5g/day Oral	-	Exercise time	-	
Fujiwara (1991)	30	>30days	IV 60mg/kg	Coronary flow	-	-	-
Lagioia (1992)	12	15days	1.5g/day	-	total work exercise time to ischaemia	-	-
Bartels (1992)	32	Smin-infusion	15mg/kg	Contractbility relaxation lactate uptake			
Polazzuoli (1993)	30	15days	Oral 6g/day	-	-	PVC	Improved status
Iliceto (1995)	472	1 year	6g/day Oral	EDV and ESV	-	-	Improved status
Singh (1996)	101	28days	2g/day Oral	LVF		PVC	Angina

LVEDP = Left ventricular end diastolic pressure
IV = Intravenous, EDV= End diastolic volume, ESV-End systolic volume,
LVF = Left ventricular failure.

seizures, hepatomegaly, skeletal muscle weakness are common in association with cardiomyopathy. Histological examination of myocardial, skeletal-muscle or hepatic tissue from patients with systemic carnitine deficiency has shown increased lipid deposition and abnormal aggregated mitochondria. Hypoglycemia, hyperammonia and recurrent episodes of acidosis are usual metabolic abnormalities.

Carnitine supplementation in patients with cardiopathy is usually associated with rapid beneficial effects characterised by improvement in cardiac function[20-23]. In one 5.5 year old boy, left ventricular ijection fraction increased from 39% to 75% after only one month of treatment with L-carnitine[20]. Clinical benefits in cardiac function in carnitine treated patients may be reduction in heart size and heart failure and reduction in the amplitude of T-waves recorded in the precordial leads.

In one double blind study[22], the haemodynamic effects of L-carnitine were studied in 34 patients with dilated cardiomyopathy and heart failure. After one month treatment with placebo (Gr. A, 18) and L-carnitine (Gr B, 16), right cardiac catheterization and cardiopulmonary exercise tests were repeated. The data suggested that L-carnitine group showed a beneficial haemodynamic effect on cardiopulmonary exercise test, peak or consumption, arterial/pulmonary blood pressure and cardiac output. In severe heart failure, carnitine supplementation can also decrease plasma renin activity. It may also reverse cardiomyopathy associated with renal tubular waisting and modulate dyslipidemia[23,24].

Carnitine administration:

Carnitine may be administered eitther through the foods rich in carnitine or as a drug[1-3]. Red meat, milk and milk products are rich sources of carnitine. It is possible that foods rich in lysine and methionine which are important for biosynthesis of carnitine may also increase carnitine reserve on increased intake of these foods. In USA, carnitine is available as health food. Since carnitine occurs endogenously, its pharmacokinetic properties can only be studied under controlled conditions that give due consideration to dietary intake and baseline serum and urine levels[1-3].

After intravenous administration, serum levels of carnitine rise rapidly and can go upto 1612um/L which is 36 times higher than normal values[3]. Serum levels generally return to near baseline levels approximately 12 hours post-infusion. The intravenous dose is 40-60mg/kg body weight per day. After oral administration of 2- 6g of L-carnitine, the rise in serum levels is gradual and peak levels are achieved between 3-9 hours[3]. Carnitine is excreted in urine.

The recommended oral dosage for treatment of primary systemic deficiency in adults is 2g/day in divided doses. Infants and children may be given 50-100mg/kg/day in divided doses, upto a maximum of 3g/day. The optimal dose of carnitine for management of other cardiovascular disorders has not yet been established. Propiony1 carnitine was developed for transport into myocardium and acetyl carnitine for transport into brain which may be more effective. In different studies, L-carnitine has been given in doses of 1-4g/day in patients with CAD for oral use and 1-2g intravenously. In India L-carnitine is marketed as tablet (330mg) or syrup (500mg- in each 5ml).

Adverse effects:

Adverse reactions that have been observed, consist of mild gastrointestinal complaints such as nausea, vomiting, diarrhoea and abdominal cramps[3,17]. These effects usually resolve with a reduction in carnitine dosage. There have been no reports of toxicity from carnitine overdosage. The oral LD50 of Levo-carnitine in mice is 19.2g/day. There are no drug interactions.

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