AUCTORES
Globalize your Research

International Journal of Biomed Research

Aamir Jalal Al Mosawi *

Open Access

Review Article

The uses of L-Carnitine in cardiology

Aamir Jalal Al Mosawi
Advisor Doctor, Baghdad Medical City and the National Center for Training and Development of Iraqi Ministry of Health, Iraq
Corresponding Author: Aamir J. A. Mosawi. Advisor Doctor,Baghdad Medical City and the National Center for Training and Development of Iraqi Ministry of Health, Iraq

Received date: March 01, 2021 **Accepted date:** March 12, 2021 **Published date:** March 16, 2021
Citation: Aamir J. A. Mosawi (2021) The uses of L-Carnitine in cardiology. *International Journal of Biomed Research.* 1(1). DOI: 10.31579/IJBR-2021/006

Abstract

L-carnitine is a non-protein amino acid synthesized from the essential amino acids lysine and methionine or obtained from dietary sources. Accumulating scientific research evidence suggests that L-carnitine has beneficial cardiovascular effects, and a potential in the management of a variety of cardiovascular disorders including congestive heart failure. The aim of this paper is to review the uses of L-Carnitine in cardiology.

Conclusion: Chronic heart diseases remain an important cause of morbidity and mortality in Iraq and many other countries in the world suggesting a need for advancing their medical therapy, possibly through emphasis on impairment in substrate metabolism and heart energy and substrate utilization which contribute to contractile dysfunction, and not expected to improve with traditional therapies. Fat is the most important energy source for heart muscle , and carnitine is vital for normal fatty acid beta-oxidation, and inadequate carnitine can cause cardiac dysfunction.

There is convincing evidence from experimental and clinical research that L-Carnitine has a beneficial effect when used in the treatment of a variety of heart diseases including congestive heart failure, myocardial infarction, and angina. The effect of L-Carnitine can be attributed to cardio-protective effects against ischemia and increasing the rate of fatty acid transport into mitochondria. It can improve exercise tolerance and oxygen consumption leading to symptomatic improvement and mortality reduction. As an anti-anginal agent, it can reduce ST segment depression and left ventricular end-diastolic pressure. L-Carnitine can also improve myocardial ischemia by relieving inhibition of mitochondrial adenine nucleotide translocase.

Key words: l-carnitine, cardiology, heart disease

L-carnitine is a non-protein amino acid synthesized from the essential amino acids lysine and methionine or obtained from dietary sources. There are two main natural forms of L-carnitine, Acetyl-L-carnitine and propionyl-L-carnitine. Physiological roles of L-carnitine include [1-12]:

1-L-carnitine has an important role in fatty acid metabolism as it is an essential cofactor of carnitine palmitoyltransferanse 1 (CPT1), which allows fatty acid transport into mitochondria and the incorporation of long chain fatty acids into the β-oxidation cycle to obtain acetyl-CoA.

2-L-carnitine has an important role in glucose metabolism through as modulates the intra-mitochondrial acetyl-CoA/CoA ratio and the pyruvate dehydrogenase complex (PDH).

3-L-carnitine reduces the accumulation of the intermediate products of β-oxidation by increasing the efflux of acyl and acetyl groups (acyl-carnitines and acetyl-carnitine) out of cells into the plasma.

Failure of this physiologic role with the accumulation of β-oxidation intermediates may contribute to the development of insulin resistance in heart and skeletal muscle and of heart failure and ischemia.

Therefore, L-carnitine supplementation may have beneficial effects in the treatment of insulin resistance and cardiovascular diseases, by restoring tissue carnitine of skeletal muscle and myocardium.

4-L-carnitine helps cardiomyocytes in meeting their absolute need for ATP, and thus preserving the pulsatile cardiac function, and help in maintaining cell and tissue viability.

As early as 1960s, experimental evidence from animal study on guinea pigs suggested abnormal metabolism of long chain fatty acids in heart failure associated with chronic constriction of the ascending aorta. Theses abnormalities were attributed to reduction in the level of myocardial carnitine which controls the oxidation rate of long chain fatty acids, a decrease in palmitic acid oxidation, and increased rate of palmitate incorporation into triglycerides and lecithin. Wittels and Spann (1968) exogenous carnitine can restore defective palmitate metabolism [1].

Morand et al (1979) reported the occurrence of lipidic myopathy diagnosed by muscle biopsy and associated with severe cardiomyopathy caused by a generalized carnitine deficiency in a girl who presented initially with nausea, vomiting and intermittent hypoglycemia. At the age of five years, the girl developed generalized muscular weakness with severe amyotrophy, and cardiomegaly. Thereafter, she developed severe heart failure. Treatment with carnitine chlorhydrate and a diet low in lipids and high in medium chain triglycerides was associated with rapid improvement in myopathy and heart failure [2].

Early during the 1980s, the occurrence of myocardial carnitine deficiency in chronic heart failure has been emphasized, and the possibility of using carnitine in heart failure has been suggested. A role in the prevention of arrhythmias in acute myocardial infarct has also been suggested (Lanni et al, 1980; Suzuki et al, 1982) [3, 4, 5].

Experimental evidence from animal study on hamster, suggested that cardiomyopathy associated with congestive heart failure resulting from carnitine deficiency (York and colleagues, 1983) [6].

Ramos et al (1983) reported a protective effect of carnitine in patients with diphtheric myocarditis in a controlled study which included 132 diphtheric patients, 73 patients of them were treated with DL-carnitine, 100 mg/kg/day during 4 days after hospitalization. Treatment reduced the incidence of heart failure (P = 0.0475), of pacemaker implants (P = 0.0256), and of lethality indexes due to myocarditis (P = 0.013) [7].

Experimental evidence from animal study on turkeys with spontaneous cardiomyopathy and turkeys with furazolidone-induced cardiomyopathy associated with heart failure suggested that liver synthesis of carnitine increases in response to hypotension to promote beta-oxidation of fatty acids as a cardiac energy source (Pierpont et al, 1985) [8].

Ghidini et al (1985) reported a controlled study which included 38 patients (22 men, 16 women) with heart failure, secondary to ischemic and/or hypertensive heart disease. Their age raged from 65 to 82 years. Treatment included digitalis, diuretics, and antiarrhythmic agents). 21 patients received also oral L-carnitine 1-g doses twice daily for 45 days, while 17 received placebo. L-carnitine treatment resulted in a distinct improvement with reduced heart rate, edema and dyspnea, and increased diuresis and a marked reduction in daily digitalis requirement. L-carnitine treatment was also associated with a significant lowering of cholesterol and triglyceride levels, and was not associated with adverse effects in any patient [9].

A double-blind clinical study reported the treatment of 115 patients with septic, cardiac and traumatic shock, with bolus intravenous dose of acetyl-L-carnitine followed by infusion for 12 hours. Treatment was associated with improvement in blood oxygenation and significant reduction in heart rate and right atrial pressure in patients cardiogenic shock. In patients with septic shock, treatment increased systolic and mean arterial pressures (Gasparett et al, 1991) [10].

Kobayashi and colleagues (1992) treated patients with ischemic heart disease with oral L-carnitine for 12 weeks. Treatment was associated with significant improvement in exercise tolerance of patients with effort angina. Of 9 treated patients with chronic congestive heart failure, 5 patients (55%) moved to a lower NYHA class and the overall condition was improved in 6 patients (66%) [11].

Fernandez and Proto (1992) reported that treatment of patient with chronic myocardial ischemia with 2 g daily of L-carnitine during 1 year was associated with lowering of rate of anginal pains, reducing the requirement of nitrates, and also improvement of physical performance [12].

Bartels (1992) emphasized the importance of myocardial carnitine content in controlling myocardial oxidative metabolism and energy transfer. They used L-propionylcarnitine, a potent analogue of L-carnitine in attempt to improve heart function through a possible positive inotropic effect in 32 fasting normotensive patients with coronary artery disease. They treated sixteen patients with L-propionylcarnitine (15 mg/kg), while sixteen control patients received a vehicle mannitol/acetate, infused over five minutes.

In the control group, heart contractility was reduced by 5% with a significant 11% reduction in stroke volume. While patients treated L-propionylcarnitine didn't experience change in isovolumetric contractility indices, but the peak ejection and filling rates improved by 16% at 45 minutes. In addition, the cardiac output in the treated patients increased by 8%. However, treatment had no effect systemic or coronary hemodynamics and myocardial oxygen consumption, but lactate uptake increased by 42%. [13]

Mancini et al (1992) reported a controlled study which included 60 patients (48 and 73 years) with mild to moderate (II and III NYHA class) congestive heart failure whom were treated with digitalis and diuretics for at least three months, but remained symptomatic. Thirty patients were additionally treated with oral mg of propionyl-L-carnitine, three times a day for 180 days. After one month, treatment was associated with significant increases in the maximum exercise and ventricular ejection fraction. Accordingly, Mancini et al thought that propionyl-L-carnitine has undoubted therapeutic benefit in patients with congestive heart failure, and it can be efficaciously added to the standard therapy [14].

Pucciarelli et al (1992) reported a controlled study which included 50 patients (48-69 years) with mild-moderate congestive heart failure and were treated with digitalis and diuretic. 25 patients were treated with oral propionyl-L-carnitine 2 g in two divided doses. Treatment increased maximum exercise time on the treadmill increased 11.1% after 90 days and 16.4% after 180. After 30, 90 and 180 days, the ejection fraction increased by 7.3%, 10.7% and 12.1%.In addition, the systemic vascular resistances were reduced by 14.9%, 20% and 20.6%.Control patients didn't experience significant changes. Just like, Mancini et al, Pucciarelli et al suggested that propionyl-L-carnitine can be beneficially and safely added to the standard therapy of congestive heart failure [15].

Iliceto et al (1995) emphasized that carnitine has an essential role in myocardial energy production at the mitochondrial level, and myocardial carnitine deficiency occurs during ischemia, acute myocardial infarction and cardiac failure. Accordingly, carnitine supplementation is associated with beneficial effect on heart function in these cardiac conditions.

Iliceto et al reported a randomized, double-blind, placebo-controlled, multicenter trial which included 472 patients with a first acute myocardial infarction and high quality two-dimensional echocardiograms. 233 patients were treated with L-carnitine within 24 hours of the onset of chest pain, while 239 control patients received either placebo. L-carnitine was given at a dose of 9 g/day intravenously for the first 5 days and then 6 g/day orally for the next 12 months.

A significant attenuation of left ventricular dilation in the first 12 months after acute myocardial infarction was reported in patients treated with L-carnitine compared with the control patients. The initially increased end-diastolic and end-systolic volumes were also significantly reduced in the L-carnitine treated patients. No significant differences were observed in left ventricular ejection fraction changes over time in the two groups. The combined incidence of congestive heart failure and death after discharge was 14 patients (6%) in the treatment group, and 23 (9.6%) in the placebo group (p = NS). However, the incidence of ischemic events during follow-up was similar in the treatment and control groups.

Therefore, early and long-term L-Carnitine treatment following acute myocardial infarction can lessen left ventricular dilation during the first year following an acute myocardial infarction, resulting in smaller left ventricular volumes [16].

Singh et al (1996) reported a randomized, double-blind placebo-controlled trial which included 101 patients with suspected acute myocardial infarction. 51 patients treated with oral L-carnitine 2 g daily for four weeks and 50 patients treated with placebo. After treatment, the mean infarct size evaluated by cardiac enzymes was significantly less in the treated patients. QRS-score on electrocardiography was also significantly less in the in the treated patients. In addition, serum aspartate transaminase and lipid peroxides were significantly lower in the treated patients. Lactate dehydrogenase measured on the sixth or seventh day after infarction showed less increase in the treated patients. Angina

pectoris, New York Heart Association class III and IV heart failure plus left ventricular enlargement and total arrhythmias were significantly less in the treated patients. Cardiac deaths and nonfatal infarction occurred in 15.6% in the treated patients, while it occurred in 26.0% in patients who received placebo. Singh et al that L-carnitine supplementation in patients with suspected acute myocardial infarction can have protective effect against cardiac necrosis and complications during the first four weeks [17].

Kawasaki et al (1996) reported an experimental study on eight-week-old male Sprague-Dawley rats which showed that maintaining myocardial level of carnitine with use of L-carnitine treatment can delay death of rats with adriamycin-induced failure by improving the myocardial metabolism of fatty acids [18].

Ferrari and De Giuli (1997) highlight some experimental studies suggesting that L-carnitine is potentially beneficial in the treatment of congestive heart failure because of its effects on heart and skeletal muscle which include improving energy metabolism and myocardial contractility. Chronic treatment with propionyl-L-carnitine was reported to improve the contraction of isolated and aerobic perfused rabbit hearts, pressure-overloaded rats, infarct model of heart failure, and rabbit with streptozotocin-induced diabetes. According to Ferrari and De Giuli, the available experimental evidence suggests that propionyl-L-carnitine treatment of patients with congestive heart failure can improve skeletal muscle metabolism by increasing pyruvate flux into the Krebs cycle, and by lowering lactate production. Therefore, propionyl-L-carnitine can increase exercise performance in patients with heart failure [19].

Näveri et al (1997) reported skeletal muscle metabolic response to maximal bicycle exercise in a study which included ten patients with chronic congestive heart failure and nine healthy individuals. They found that the important limiting factor of exercise performance during heavy exercise in congestive heart failure and healthy individuals, is a high rate of skeletal muscle lactate accumulation and high-energy phosphate depletion. In patients with congestive heart failure, the low activity of aerobic enzymes impairs energy production and cause lactate acidosis at lower workloads [20].

Anand et al (1998) reported treating 30 patients with chronic congestive heart failure with IV bolus of propionyl-L-carnitine 30 mg/kg body weight, and chronic intake (1.5 mg daily for 1 month). The with IV bolus of propionyl-L-carnitine resulted in a significant reduction in pulmonary artery and pulmonary wedge pressures at day 1 ($P < 0.001$), and day 30 ($P < 0.05$) of treatment without causing other hemodynamics changes. Chronic intake of propionyl-L-carnitine was associated with a 45% increase in peak oxygen consumption, exercise time by 21%, and in peak exercise heart rate by 12%. There was also a decrease in pulmonary artery pressure. Treatment was also associated with a slight, but significant ($P < 0.01$), reduction in left ventricular dimensions. The chronic changes resulted from treatment were observed at 15 days of treatment, but no more changes observed at one month. Anand et al suggested that propionyl-L-carnitine increases exercise capacity and reduces ventricular size in patients with congestive heart failure [21].

Rizos (2000) reported a controlled study which included 80 patients with moderate to severe heart failure (New York Heart Association classification III to IV) caused by dilated cardiomyopathy. Treatment group received oral L-carnitine 2 grams daily for one year. After a follow-up period ranging from 10 to 54 months, 70 patients including live 63 patients were in the study. 33 patients were in the placebo group and 37 patients were in the treatment group. Six deaths occurred in the placebo group and one death in the treatment group. Survival analysis with the Kaplan-Meier method revealed that patients' survival was statistically significant ($P <.04$) in favor of the treatment group. The study of Rizos emphasized that L-carnitine has the potential for the long-term treatment of patients with heart failure caused by dilated cardiomyopathy [22].

Tarantini et al (2006) suggested that the use of L-carnitine therapy in the treatment of acute anterior ST segment elevation myocardial infarction can reduce early mortality without affecting the risk of death and heart failure at six months in patients [23].

Bugger et al (2010) reported an experimental study on Sprague-Dawley rats which showed that pressure overload-induced heart failure is associated with a considerable defect in heart oxidative capacity cause partly by a mitochondrial defect downstream of substrate-specific pathways [24].

Serati et al (2010) reported a controlled study which included 60 patients with diastolic heart failure. 29 patients of them were treated with 1.5 g of L-carnitine daily for three months. Important parameters of diastolic dysfunction (Left atrial size, isovolemic relaxation time, septal mitral E velocity, and lateral mitral E velocity) improved in the treated patients only. Dyspnea also considerably improved in the treated patients only [25].

Xu et al (2010) reported a controlled study which included 66 patients with pulmonary arterial hypertension (14 idiopathic, 36 congenital heart disease associated and 16 connective-tissue disease associated PAH, WHO heart functional class III, n = 38 or IV, n = 28). All the patients were treated with traditional therapies of right-sided heart failure. Forty patients were treated with L-carnitine 5 g daily intravenously for seven days. Treatment was associated with a significant increase in the six-minute walking distance and significant improvement in WHO heart functional class [26].

Omori et al (2012) reported an experimental study on Dahl rats hypertensive HFpEF model. L-carnitine supplementation lessened cardiac fibrosis by increasing prostacyclin production through arachidonic acid pathway [27].

Cheng and Tang (2013) reported a controlled study which included 120 elderly patients with chronic heart failure whom were treated with traditional therapies.

Sixty patients also received 3 g levocarnitine within 250 ml normal saline intravenous infusion for 15 days. Levocarnitine significantly improved the heart function, and treatment effectiveness was significantly higher than in the control group [28].

Song et al (2017) reported a meta-analysis of randomized controlled trials which included seventeen trials with 1625 congestive heart failure patients. L-carnitine treatment was associated with significant improvement in overall efficacy, clinical symptoms, cardiac functions, left ventricular ejection fraction, and cardiac output. L-carnitine treatment was also associated with a good tolerance [29].

Moreira et al (2018) emphasized the intense aerobic cardiac metabolism which necessitates storing fatty acid, the chief energetic substrate, and also demands high concentrations of plasma L-carnitine to facilitate the transport of fatty acids to the mitochondria to generate energy. Moreira et al reported a cross-sectional study which included 109 patients with chronic heart failure. Low plasma L-carnitine was found in 29.1% of patients who were found to have decompensated heart failure group [30].

Wang et al (2018) reported 29 children with dilated cardiomyopathy (17 male, 12 female and aged 1 month to 13 years) whom were treated with oral hydrochlorothiazide, enalapril, and spironolactone. Patients with cardiac function of NYHA grade IV were also given oral digoxin, and patients with intractable heart failure were also given intravenous dopamine and dobutamine. When cardiac function was restored to NYHA grade II-III, patients were given oral metoprolol. Nineteen of the 19 received add-on treatment with oral levocarnitine solution (50-100 mg/kg/day).Heart function was significantly improved in the patients treated with levocarnitine with increased left ventricular ejection fraction, and reduction of the left atrium and left ventricle diameters [31].

Shahidi et al (2020) reported a randomized clinical study which included sixty β-thalassemia patients, 30 patients were treated with L-carnitine for six month. Treatment was associated with a reduction left ventricular dilatation, left ventricular hypertrophy, and systolic blood pressure. Treatment also improved cardiac output from 43.5 to 56.5 (P=0.002) [32].

References

1. 1-Wittels B, Spann JF Jr.(1968) Defective lipid metabolism in the failing heart. J Clin Invest ; 47(8):1787-94. Doi: 10.1172/JCI105868. PMID: 4233124.
2. Morand P, Despert F, Carrier HN, Saudubray BM, Fardeau M, Romieux B, Fauchier C, Combe P. (1979)Myopathie lipidique avec cardiomyopathie sévère par déficit généralisé en carnitine. Evolution favorable sous un traitement par chlorhydrate de carnitine [Lipidic myopathy with severe cardiomyopathy caused by a generalized carnitine deficiency. Favourable course during carnitine hydrochloride treatment]. Arch Mal Coeur Vaiss. May; 72(5):536-44. PMID: 115407 [Article in French].
3. Giordano MP, Roncarolo PL, Gabasio CA, Corsi M, Trevisani C. L'acetil (1981) carnitina nella prevenzione delle complicazioni aritmiche in corso di infarto miocardico acuto. Risultati preliminari [Acetyl carnitine in the prevention of arrhythmic complications in acute myocardial infarct. Preliminary results]. Minerva Cardioangiol May; 29(5):241-6. PMID: 7254540 [Article in Italian].
4. Suzuki Y, Masumura Y, Kobayashi A, Yamazaki N, Harada Y, Osawa M. Myocardial(1982) carnitine deficiency in chronic heart failure. Lancet.; 1(8263):116. Doi: 10.1016/s0140-6736(82)90263-x. PMID: 6119489.
5. Lanni N, Chiumiento P, Pannella G, Grimaldi U, D'Auria M, Imbimbo N. Impiego (1980)della carnitina nella terapia dell'insufficienza cardiaca: contributo clinico [Use of carnitine in cardiac insufficiency: clinical contribution]. Clin Ter Nov 15; 95(3):305-12. PMID: 7214846 [Article in Italian].
6. York CM, Cantrell CR, Borum PR. (1983)Cardiac carnitine deficiency and altered carnitine transport in cardiomyopathic hamsters. Arch Biochem Biophys Mar; 221(2):526-33. Doi: 10.1016/0003-9861(83)90171-6. PMID: 6838206.
7. Ramos AC, Elias PR, Barrucand L, Da Silva JA. (1984)The protective effect of carnitine in human diphtheric myocarditis. Pediatr Res Sep; 18(9):815-9. Doi: 10.1203/00006450-198409000-00001. PMID: 6483504.
8. Pierpont ME, Judd D, Borgwardt B, Noren GR, Staley NA, Einzig S.(1985) Carnitine alterations in spontaneous and drug-induced turkey congestive cardiomyopathy. Pediatr Res. May; 19(5):415-20. Doi: 10.1203/00006450-198505000-00001.PMID: 400076 6.
9. Ghidini O, Azzurro M, Vita G, Sartori G.(1988) Evaluation of the therapeutic efficacy of L-carnitine in congestive heart failure. Int J Clin Pharmacol Ther Toxicol Apr; 26(4):217-20. Erratum in: Int J Clin Pharmacol Ther Toxicol 1989 Aug; 27(8):418. PMID: 3403101.
10. Gasparetto A, Corbucci GG, De Blasi RA, Antonelli M, Bagiella E, D'Iddio S, Trevisani C.(1991) Influence of acetyl-L-carnitine infusion on haemodynamic parameters and survival of circulatory-shock patients. Int J Clin Pharmacol Res; 11(2):83-92. PMID: 1879992.
11. Kobayashi A, Masumura Y, Yamazaki N. L-carnitine(1992) treatment for congestive heart failure--experimental and clinical study. Jpn Circ J Jan; 56(1):86-94. Doi: 10.1253/jcj.56.86. PMID: 1538579.
12. Fernandez C, Proto C. La(1992) L-carnitina nel trattamento dell'ischemia miocardica cronica. Analisi dei risultati di tre studi multicentrici e rassegna bibliografica [L-carnitine in the treatment of chronic myocardial ischemia. An analysis of 3 multicenter studies and a bibliographic review]. Clin Ter. Apr; 140(4):353-77. PMID: 1534043 [Article in Italian].
13. Bartels GL, Remme WJ, Pillay M, Schönfeld DH, Cox PH, Kruijssen HA,(1992) Knufman NM. Acute improvement of cardiac function with intravenous L-propionylcarnitine in humans. J Cardiovasc Pharmacol Jul; 20(1):157-64. PMID: 1383625.
14. Mancini M, Rengo F, Lingetti M, Sorrentino GP, Nolfe G.(1992) Controlled study on the therapeutic efficacy of propionyl-L-carnitine in patients with congestive heart failure. Arzneimittelforschung Sep; 42(9):1101-4. PMID: 1445476.
15. Pucciarelli G, Mastursi M, Latte S, Sacra C, Setaro A, Lizzadro A, Nolfe G.(1992) Effetti clinici ed emodinamici della propionil-L-carnitina nel trattamento dello scompenso cardiaco congestizio [The clinical and hemodynamic effects of propionyl-L-carnitine in the treatment of congestive heart failure]. Clin Ter. Nov; 141(11):379-84. PMID: 1493661 [Article in Italian].
16. Iliceto S, Scrutinio D, Bruzzi P, D'Ambrosio G, Boni L, Di Biase M, Biasco G, Hugenholtz PG, Rizzon P.(1992) Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial. J Am Coll Cardiol x Aug; 26(2):380-7. Doi: 10.1016/0735-1097(95)80010-e. PMID: 7608438.
17. Singh RB, Niaz MA, Agarwal P, Beegum R, Rastogi SS, Sachan DS. A randomised, (1996) double-blind, placebo-controlled trial of L-carnitine in suspected acute myocardial infarction. Postgrad Med J Jan; 72(843):45-50. Doi: 10.1136/pgmj.72.843.45. PMID: 8746285.
18. Kawasaki N, Lee JD, Shimizu H, Ueda T.(1996) Long-term 1-carnitine treatment prolongs the survival in rats with adriamycin-induced heart failure. J Card Fail;2(4):293-9. Doi: 10.1016/s1071-9164(96)80016-9. PMID: 8989644.
19. Ferrari R, De Giuli F. The propiony(1997)l-L-carnitine hypothesis: an alternative approach to treating heart failure. J Card Fail Sep;3(3):217-24.Doi: 10.1016/s1071-9164(97)90018-x. PMID: 9330130.
20. Näveri HK, Leinonen H, Kiilavuori K, Härkönen M.(1997) Skeletal muscle lactate accumulation and creatine phosphate depletion during heavy exercise in congestive heart failure. Cause of limited exercise capacity? Eur Heart J Dec;18(12):1937-45. Doi:10.1093/oxfordjournals.eurheartj.a0 15203. PMID: 9447322.
21. Anand I, Chandrashekhan Y, De Giuli F, Pasini E, Mazzoletti A, Confortini R, Ferrari R.(1998) Acute and chronic effects of propionyl-L-carnitine on the hemodynamics, exercise capacity, and hormones in patients with congestive heart failure. Cardiovasc Drugs Ther Jul;12(3):291-9. Doi: 10.1023/a:1007721917561. PMID: 9784909.
22. Rizos I.(2000) Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J Feb;139(2 Pt 3):S120-3. Doi: 10. 106 7/ mhj. 20 00.103917. PMID: 10650325.
23. Tarantini G, Scrutinio D, Bruzzi P, Boni L, Rizzon P, Iliceto S.(2006) Metabolic treatment with L-carnitine in acute anterior ST segment elevation myocardial infarction. A randomized controlled trial. Cardiology.;106(4):215-23. Doi: 10.1159/000093131. PMID: 16685128.
24. TD, Mohr FW, Khalimonchuk O, Weimer BC, Doenst T. (2010) Proteomic remodelling of mitochondrial oxidative pathways in pressure overload-induced heart failure. Cardiovasc Res Jan 15; 85(2):376-84. Doi: 10.1093/cvr/cvp344. PMID: 19843514.
25. Serati AR, Motamedi MR, Emami S, Varedi P, (2010) Movahed MR. L-carnitine treatment in patients with mild diastolic heart failure is associated with improvement in diastolic function and

symptoms. Cardiology;116(3):178-82. Doi: 10.1159/000318810. PMID: 20639632.
26. Xu XQ, Jing ZC, Jiang X, Zhao QH, He J, Dai LZ, Wu WH, Li Y, Yao J. (2010) [Clinical efficacy of intravenous L-carnitine in patients with right-sided heart failure induced by pulmonary arterial hypertension]. Zhonghua Xin Xue Guan Bing Za; 38(2):152-5. PMID: 20398563 [Article in Chinese].
27. Omori Y, Ohtani T, Sakata Y, Mano T, Takeda Y, Tamaki S, Tsukamoto Y, Kamimura D, Aizawa Y, Miwa T, Komuro I, Soga T, Yamamoto K. (2012) L-Carnitine prevents the development of ventricular fibrosis and heart failure with preserved ejection fraction in hypertensive heart disease. J Hypertens:1834-44. Doi: 10.1097/HJH.0b013e3283569c5a. PMID: 22796714.
28. Cheng L, Tang XF. (2013) [Influence of levocarnitine on heart function and endocrine among patients with heart failure]. Zhonghua Liu Xing Bing Xue Za Zhi.;34(6):630-2. PMID:24125620 [Article in Chinese].
29. Song X, Qu H, Yang Z, Rong J, Cai W, Zhou H. (2017) Efficacy and Safety of L-Carnitine Treatment for Chronic Heart Failure: A Meta-Analysis of Randomized Controlled Trials. Biomed Res Int;2017:6274854. Doi: 10.1155/2017/6274854. PMID: 28497060.
30. Moreira da Silva Guimarães S, de Souza Cruz WM, de Souza Weigert G, Scalco FB, Colafranceschi AS, Ribeiro MG, Boaventura GT. (2018) Decompensated Chronic Heart Failure Reduces Plasma L-carnitine. Arch Med Res;49(4):278-281.Doi: 10.1016/j.arcmed.2018.09.004 .PMID: 30268703.
31. Wang Y, Xu Y, Zou R, Wu L, Liu P, Yang H, Xie Z, Wang C. (2018) Effect of Levocarnitine on the therapeutic efficacy of conventional therapy in children with dilated cardiomyopathy: Results of a randomized trial in 29 children. Paediatr Drugs:285-290.Doi:10.1007/s402 72-018-0284-2. PMID: 29468383.
32. Shahidi M, Hashemi SR, Fattahi N, Roshani D, Vahedi S, Sharifi P, Moradveisi B. (2020) The Effects of L-Carnitine on Echocardiographic Changes in Patients With β-Thalassemia major and intermedia. J Pediatr Hematol Oncol Aug; 42(6):386-390.

DOI: 10.31579/IJBR-2021/006