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Effect of L-Carnitine on the Physical Fitness of Thalassemic Patients

AMAL EL-BESHLAWY, M.D.*; MANSOUR ABD EL-SATTAR, M.D.**;
MOHAMED HANY GAMAL EL-DEEN, M.D.***; ILHAM YOUSSRY, M.D.*;
NAGLAA SHAHEEN, M.D.*; MONA HAMDY, M.D.* and MONA EL-GHAMRAWY, M.D.*

The Departments of Pediatrics, New Children Hospital, Cairo University; Al-Azhar University** and Physiology, Cairo University****.*

ABSTRACT

Introduction: Poor physical fitness is a common problem among thalassemic patients. Many of these patients complain of muscular weakness and myalgia. Reduction of serum carnitine levels might play an important role in the appearance of muscular dysfunction. Moreover, cardiopulmonary diseases secondary to chronic anemia and hemosiderosis still remain a major cause of morbidity and mortality in these patients and contribute to their poor physical fitness. Chronic anemia and tissue hypoxia result in impairment of free fatty acid oxidation and ATP production. L-carnitine, a butyric acid derivative, acts as an essential cofactor in the β-oxidation of long-chain fatty acids which results in production of ATP.

Objective: To study the effect of L-carnitine therapy on exercise tolerance and physical fitness in thalassemia major patients.

Patients and Methods: Thirty patients attending the Hematology Clinic of the New Cairo University Children Hospital were included in this study. The mean age was 14.6±2.7 years. Clinical, laboratory and cardiopulmonary exercise testing were performed before and after 6 months of oral L-carnitine therapy (50mg/kg/day).

Results: In our study oxygen consumption (VO_2 max), cardiac output and oxygen pulse at maximal exercise increased significantly after L-carnitine therapy ($p<0.001$, $p<0.002$ and $p<0.001$ respectively). However, there was no significant change in minute ventilation and ventilatory equivalent of carbon dioxide ($p>0.05$). The degree of improvement in exercise parameters was higher for the younger patients. Our results also showed a significant increase in weight and height after L-carnitine therapy ($p=0.04$ and $p=0.03$ respectively). A significant increase in the interval of blood transfusion after therapy ($p=0.008$) was observed, but there was no increase in hemoglobin concentration ($p>0.05$).

Conclusion: L-carnitine seems to be an effective therapeutic approach in thalassemic patients. It improves their cardiac performance, physical fitness and general activity. Its effect on physical growth is worthy for further studies.

Key Words: *Physical fitness - L-carnitine - Thalassemia major.*

INTRODUCTION

Poor physical fitness is a common feature among thalassemic patients. It is known that children with homozygous β-thalassemia manifest a decrease in muscular mass and many of them complain of muscular weakness and myalgia **[1]**. Several interpretations have been given to justify these symptoms, including tissue anoxia, peripheral nerve disorders and abnormal calcium metabolism attributed to decreased hemoglobin and systemic hemosiderosis **[2,3]**. Moreover, cardiopulmonary affection and growth retardation still remain major problems for these patients in spite of the progress in management of β-thalassemia with chronic transfusion therapy and iron chelation **[4]**. All of the aforementioned abnormalities contribute to the poor physical fitness in these patients. Parameters of poor physical fitness include chronic ventilatory and cardiopulmonary abnormalities **[5]**.

Chronic anemia and subsequent tissue hypoxia impairs free fatty acid oxidation which is the major energy providing pathway of myocardium and its inhibition has been shown to impair myocardial function **[6]**.

L-carnitine, a butyrate analogue (3-hydroxy-4-N-trimethyl-aminobutyric acid) is a well tolerated and safe physiological compound. It

plays an essential role in fatty acid oxidation, glucose metabolism and energy production **[7]**. It is crucial to the shuttle mechanism of long chain fatty acid across the inner mitochondrial membrane, thus providing substrate for oxidation and subsequent energy production especially in those organs and tissues that preferentially use fatty acid for their energy needs as the myocardium and the skeletal muscle **[6]**.

We hereby report our results regarding the effect of L-carnitine therapy on exercise tolerance and physical fitness in 30 patients with thalassemia major followed up for 6 months in our center.

PATIENTS AND METHODS

Patients:

Thirty patients, 19 males and 11 females, with homozygous β-thalassemia attending the Hematology Clinic of the New Cairo University Children Hospital were included in this study. Their age ranged between 10-20 years with a mean of 14.6±2.7 years. All patients were on regular blood transfusion. They were all on desferoxamine chelation therapy (20-40mg/kg/day). None of the enrolled patients had chest wall deformity, cardiac, muscle, metabolic or neurological disorders.

The patients were evaluated before and 6 months after oral L-carnitine therapy (50mg/kg/day). The drug was supplied by the Hematology Clinic on an outpatient basis for free for each patient on each visit.

Clinical study of the patients included full history taking, focusing on general activity indicators as exercise tolerance, hours of sleep, school performance and sharing in social activities. Frequency of blood transfusion and chelation therapy were also recorded. Physical examination was done focusing on weight, height, heart rate, liver and spleen status.

Evaluation of Physical Fitness Using Cardiopulmonary Exercise Test:

Each patient performed an incremental cycle ergometer exercise during which work load of pedaling was increased at one minute interval.

Patient breaths room air through a pneumotachometer and expired air is continuously sampled and analyzed while heart rate is continuously recorded by a cardiac monitor. The following measurements were taken:

- Maximal oxygen consumption (VO_2 max) that is the oxygen consumption at maximal exercise.
- Minute ventilation (Ve) that is the volume of air respired per minute.
- Ventilatory equivalent for CO_2 (Ve/V_{CO2}).
- Oxygen pulse (O_2 pulse) that is the ratio of VO_2/heart rate.
- Cardiac output calculated from oxygen consumption and heart rate according to Striger et al. (1997) **[8]**.

All measurements were expressed as percentage of normal predicted values for each subject according to Wasserman et al. (1999) **[9]**.

The increment size was adjusted to each subject according to his/her age, height and weight so as patient reaches his/her maximal exercise level in around ten minutes as follows:

$$\text{Size of work load increment (watt/min)} = \frac{\text{Predicted } VO_2 \text{ max} - VO_2 \text{ of unloaded pedaling}}{100}$$

where, VO_2 of unloaded pedaling = 150+6 x weight in kg **[9]**.

Statistical Methods:

The numerical data is presented as mean ± standard deviation. Student's *t*-test (paired *t*-test) was used to compare numerical data between groups. Coefficient of correlation (*r*) was used to indicate the degree of correlation between different variables.

RESULTS

Exercise Findings:

A significant increase in VO_2 max, cardiac output and O_2 pulse after 6 months of L-carnitine therapy was found ($p<0.001$, <0.002 and <0.001 respectively). No significant changes were found in minute ventilation or in ventilatory equivalent of carbon dioxide ($p>0.05$) (Table 1, Fig. 1).

The correlation between the age of patients and the percentage change in VO_2 max, cardiac output and O_2 pulse was negative (r=0.49, 0.49 and 0.43 respectively).

Clinical and Laboratory Findings:

There was a significant increase in the mean weight and height of the patients 6 months after L-carnitine therapy (p=0.04 and 0.03 respectively). A significant increase in the interval of blood transfusion was also observed after therapy (p=0.008). However, there was no significant change in hemoglobin concentration (p>0.05) (Table 2).

Table (1): Cardiopulmonary exercise parameters before and after 6 months of L-carnitine therapy.

Parameter*	Before therapy	After therapy (50mg/kg/day)	*p* value
VO_2 max	39.1±11.6	56.7±17.1	<0.001
Cardiac output	56.6±12.1	73.2±15.1	<0.002
O_2 pulse	3.8±1.0	5.4±1.6	<0.001
Minute ventilation	56.0±15.9	60.0±16.8	>0.05
Ve/V_{CO2}	26.6±2.7	27.4±2.7	>0.05

*Expressed as percent of predicted value.

Table (2): Clinical and laboratory parameters before and after 6 months of L-carnitine therapy.

Parameter	Before therapy	After therapy (50mg/kg/day)	*p* value
Weight (Kg)	32.3±7.15	33.5±6.74	0.04
Height (cm)	140.8±15.18	141.7±15.3	0.03
Interval of blood transfusion (days)	28.6±9.27	37.3±14.89	0.008
Hemoglobin (g/dl)	7.8±0.79	7.3±0.95	>0.05

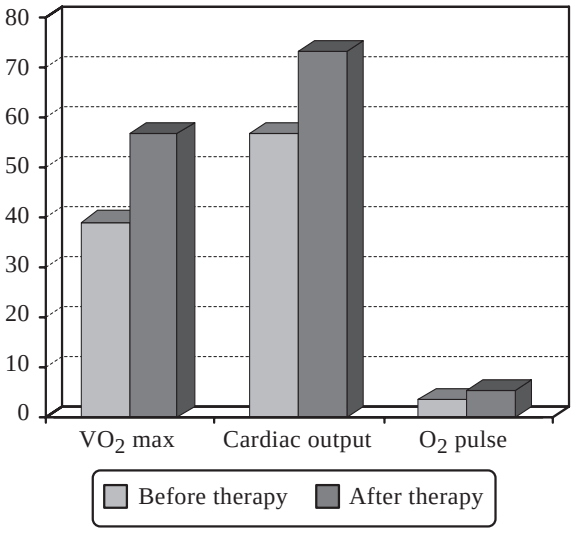

Fig. (1): Cardiopulmonary exercise parameters in thalassemic patients before and 6 months after L-carnitine.

DISCUSSION

Although current therapy for thalassemia, in the form of blood transfusion and iron chelation, has improved the prognosis of the disease, yet cardiac affection is still a major problem for these patients and muscular symptoms remain unaffected **[1,4]**.

Mitochondrial oxidation of long-chain fatty acids provides an important source of energy for the heart as well as for skeletal muscle during prolonged aerobic work. The carnitine is responsible for transferring long-chain fatty acids across the barrier of the inner mitochondrial membrane to gain access to the enzymes of beta-oxidation. Because of its key role on fatty acid oxidation, there has long been interest in the possibility that carnitine might be of benefit in energy production **[10]**.

VO_2 max is the VO_2 at which the performance of increasing levels of supra maximal work fails to increase the O_2 uptake further and this represents the highest VO_2 attainable for a given form of exercise **[11]**. There are many factors affecting VO_2 max as age, sex, physical activity, weight and height. Reduction of VO_2 max occurs in conditions with impaired O_2 flow to tissues as cardiac disease, anemia and pulmonary diseases **[9]**. In thalassemic patients, all the above mentioned conditions might contribute to a low VO_2. Anemia and cardiac dysfunction are common problems in thalassemia major. Moreover, reduction in pulmonary function tests in these patients has been reported. It was suggested that iron deposition due to repeated blood transfusion may play a central role in determining lung alterations **[12]**.

In our study, VO_2 max of thalassemic patients (expressed as percentage of their normal predicted value) was low before starting therapy. This was neither related to the degree of anemia as the hemoglobin concentration showed no significant change after treatment nor to the pulmonary state as there was no change in minute ventilation or Ve/V_{CO2} before or after therapy. However, cardiac output and O_2 pulse were low at maximum exercise. L-carnitine therapy for 6 months led to increase in VO_2 max, cardiac output and O_2 pulse. Thus improvement of VO_2 max can be attributed to improvement in cardiac function. Echocardiographic evidence of improvement of systolic

and diastolic cardiac function was shown in a study on thalassemic patients receiving L-carnitine for 2-18 months **[13]**. In another study a significant improvement of diastolic function demonstrated by MUGA was reported after 6 months of L-carnitine therapy **[14]**. Improvement in exercise capacity and VO_2 max in patients with heart failure treated with L-carnitine was reported. L-carnitine therapy appears to be particularly effective in correcting the exertion fatigue and shortness of breath that many patients continue to experience despite optimal treatment of heart failure **[15,16]**.

The most important factors that contribute to cardiac complications in thalassemic patients are chronic hypoxia and iron overload. Cardiac ischemia or hypoxemia causes striking changes in free fatty acid metabolism, inhibition of β oxidation and reduced transport of free fatty acid into the mitochondria. Inhibition of lipid metabolism results in accumulation of oxidative intermediates such as long chain acyl CoA esters that impair cardiac metabolic and mechanical function **[17]**. Iron overload leads to increased lipid peroxidation, mitochondrial membrane damage, lysosomal fragility and release of lysosomal enzymes. On the long run, fibrosis of the myocardium and specialized conductive system occurs **[18]**. Hypoxia and hemosiderosis cause myocardial damage and reduce myocardial carnitine. Exogenous carnitine therapy restores free carnitine in the myocardium and thus improves its metabolism **[19]**.

The observed improvement of cardiac function in our patients can therefore be explained by the effect of L-carnitine on myocardial energy production that is mainly covered by free fatty acids oxidation (60-90% of ATP production) **[6]**. L-carnitine therapy restores free carnitine in myocardial tissues with subsequent inhibition of accumulation of mitochondrial long chain acyl carnitine with concomitant improvement of myocardial metabolism **[20]**.

However, it has been reported that the benefit of L-carnitine therapy on myocardial mechanical function can be ascribed to the increase in overall glucose utilization rather than normalization of fatty acid metabolism **[21]**.

Moreover, L-carnitine therapy was found to strongly reduce the elevated plasma renin activity in patients with heart failure **[15]**.

On the other hand, L-carnitine improves oxidative metabolism of skeletal muscles that may indirectly improve cardiac performance as a result of a lower myocardial oxygen demand at sub-maximal exercise workload **[20]**.

In our study, all our patients showed improvement in their general activity in the form of increased exercise tolerance, decreasing sleep hours, better scholastic achievement and better sharing with social activity after therapy. Similar findings were reported in a study on the effect of L-carnitine (100mg/kg/day) for 1 month on 54 thalassemic patients, 23 of whom had myalgia and easy fatigability. L-carnitine therapy had caused remission of muscular symptoms and improvement of their quality of life **[22]**. Reduction of serum carnitine levels in thalassemic patients was also reported and it was suggested that this might play an important role in the appearance of muscular dysfunction and the clinical symptoms as myalgia and muscle weakness. L-carnitine administration in these patients might improve or even resolve these symptoms **[1]**. It has been found that it improves the skeletal muscle metabolism, increases pyruvic acid consumption and decreases lactic acid production **[23]**.

The improvement in cardiac function in response to L-carnitine therapy was higher in younger patients in our study; this finding may point out the importance of starting therapy at an early age.

We observed that administration of L-carnitine (50mg/kg/day) for 6 months has significantly increased the weight and height of our patients. In a study on the effect of L-carnitine on growth in 18 patients for duration of 6 months, a significant increase in growth velocity and a proportionate increase in the upper and lower segments were found. The increase in height was more than the increase in weight among our patients. It was concluded that carnitine has a positive effect on growth of the patients even on low hemoglobin level and bad chelation therapy **[24]**.

The positive effect of L-carnitine on growth can be explained by its effect on energy production in vital organs that depend on free fatty acid metabolism as the liver, heart and brain **[25]**. Improvement in erythrocytes survival and decreased iron deposition in different tissues can also be contributing factors **[26]**.

In this study a significant increase in blood transfusion interval after L-carnitine therapy was also observed. This was previously reported **[14,26]** and can be explained by the protective effect of L-carnitine on the erythrocytes from oxidative stress and its stabilization to the red cell membrane in which latent peroxidative damage has been produced **[27]**. Increased in vivo lipid peroxidation in children with β-thalassemia major has been shown **[28]**. The autoxidaton of globin chains and iron overload were the suggested mechanisms for the increased oxidative stress. The counteracting effect of antioxidants on lipid peroxidation processes and their protective effect against oxidative damage of red cells in β-thalassemia patients were also confirmed **[29]**.

However, in our study there was no statistically significant increase in hemoglobin concentration after L-carnitine therapy.

In conclusion, L-carnitine seems to be an effective therapeutic approach in thalassemic patients. It improves their cardiac performance, physical fitness and general activity. The effect of L-carnitine on growth of thalassemic patients is worthy for further studies.

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