

## Exercise Tolerance in Pediatric Patients on Regular Hemodialysis and Effect of L-Carnitine

Ihab El-Hakim, Hanan Ibrahim and Amal Abd El-Halim\*

*Departments of Pediatrics and Clinical Pathology\*, Faculty of Medicine, Ain Shams University, Cairo, Egypt*

### ABSTRACT

**Background:** Peak ventilatory oxygen consumption ( $VO_2$  max), which is the maximum rate that oxygen can be taken up and consumed, is widely used to characterize exercise function and can be determined from analysis of respired gases during graded exercise. Renal failure patients undergoing chronic hemodialysis have severely impaired exercise tolerance. Several factors have been suggested to be responsible for the impairment in exercise tolerance, including the loss of muscle cross-sectional area, renal anemia, inactivity, malnutrition, impaired muscle energy production or fatty acid oxidation and carnitine deficiency. Carnitine homeostasis is abnormal in hemodialysis patients. In maintenance hemodialysis, carnitine is lost through dialytic membranes, leading in selected patients to carnitine depletion.

**Objectives:** To determine exercise capacity among the studied group of patients in comparison to healthy controls, through non invasive exercise testing. In addition, carnitine status will be evaluated among them together with detection of the effect of carnitine therapy on the exercise performance.

**Methods:** The study was conducted in the Children's Hospital, Ain Shams University. It included 11 patients with chronic renal failure on regular hemodialysis. They were 6 males and 5 females with a mean age of  $15.27 \pm 2.32$  years. They were compared to 20 healthy control subjects. They were 12 males and 8 females with a mean age of  $12.8 \pm 1.93$  years. For all subjects clinical evaluation was done in addition to assay of hemoglobin, blood urea, serum creatinine, lipid profile including total triglycerides (TG), total cholesterol (TC), HDL-cholesterol (HDL-C) and calculation of LDL-cholesterol (LDL-C). Serum carnitine was also assayed by enzymatic ultraviolet test. All subjects underwent cardiopulmonary exercise testing using Bruce walking protocol. Data obtained were exercise duration,  $VO_2$  max, RER (ratio of ventilatory  $CO_2$  production/ $O_2$  consumption) and anaerobic threshold (AT). All patients received carnitine supplementation for 5 weeks, after which lipid profile and exercise testing were re-evaluated.

**Results:** Serum carnitine was significantly lower in patients with ESRD on HD compared to controls. Supplementation of carnitine did not show any effect on lipid profile. However, carnitine therapy caused significant improvement in three of the four exercise parameters used in this study, namely exercise duration, AT and RER. A significant positive correlation between hemoglobin level and  $VO_2$  max was detected in the studied patients before therapy.

**Conclusions:** ESRD pediatric patients on HD have significant impairment in exercise performance that can affect their style of life. Carnitine deficiency is considered an important contributing factor of this exercise intolerance. Carnitine therapy, although did not affect lipid profile in the studied patients, yet proved effective in improving their exercise tolerance.

### INTRODUCTION

Renal failure patients undergoing chronic hemodialysis have severely impaired exercise tolerance. This intolerance has been reported to be as low as 50% of that measured in age-matched normal adult

subjects<sup>(1)</sup>. Several factors have been suggested to be responsible for the impairment in exercise tolerance, including the loss of muscle cross-sectional area, renal anemia, inactivity, malnutrition, impaired muscle energy production or fatty acid

oxidation and carnitine deficiency<sup>(2)</sup>.

Peak ventilatory oxygen consumption ( $\text{VO}_2$  max) which is the maximum rate that oxygen can be taken up and consumed is widely used to characterize exercise function and can be determined from analysis of respired gases during graded exercise<sup>(3)</sup>. Many investigators have used  $\text{VO}_2$  max to characterize the exercise impairment of patients with end stage renal disease (ESRD)<sup>(4)</sup>.

Carnitine homeostasis is also abnormal in this population. In maintenance hemodialysis, carnitine is lost through dialytic membranes, leading in selected patients, to carnitine depletion<sup>(5)</sup>. As carnitine is an important cofactor for muscle energy metabolism, exercise performance is found to be correlated with the total muscle carnitine content<sup>(6)</sup>.

Eventually, administration of L-carnitine to adult hemodialysis patients improves exercise capacity; energy metabolism and muscle mass<sup>(7)</sup>.

#### AIM OF THE WORK

This work was conducted to determine whether exercise capacity is significantly impaired among the studied group of pediatric chronic renal failure patients on regular hemodialysis in comparison to healthy controls through non-invasive exercise testing. In addition, carnitine status was evaluated among them together with detection of the effect of carnitine therapy on the exercise performance.

#### SUBJECTS AND METHODS

The study was conducted in Children's Hospital, Ain Shams University. It included

11 patients with chronic renal failure on regular hemodialysis in the Pediatric Dialysis Unit. They were 6 males and 5 females with a mean age of  $15.27 \pm 2.32$  years. They were dialyzed for a mean period of  $3.72 \pm 1.48$  years thrice weekly, three hours each session, using cuprophane dialyzers and acetate dialysate. They were compared to 20 healthy control subjects. They were 12 males and 8 females with a mean age of  $12.8 \pm 1.93$  years.

Exclusion criteria for the patients were:

- Marked cachexia
- Laboratory evidence of malnutrition (serum albumin and total proteins)
- Echocardiographic evidence of cardiac dysfunction
- Patients receiving lipid lowering drugs or other drugs affecting plasma lipids as beta adrenergic blocking agents.

For all subjects the following was done:

- **Full history taking** and thorough clinical examination laying stress on body weight, blood pressure, exercise tolerance and manifestations of carnitine deficiency.
- **Laboratory investigations** including
  1. Hemoglobin
  2. Blood urea using enzymatic rate method on Synchro CX5 system from BECKMAN (USA)<sup>(8)</sup>.
  3. Serum creatinine using a modified rate Jaffé method on Synchro CX5 system from BECKMAN (USA)<sup>(9)</sup>.
  4. Total triglycerides (TG) by enzymatic colorimetric test using Triglycerides liquicolor test kit from Human Gesellschaft für Biochemica und Diagnostica, Germany<sup>(10)</sup>.
  5. Serum total cholesterol (TC) by

enzymatic colorimetric test using Cholesterol liquicolor test kit from Human Gesellschaft für Biochemica und Diagnostica, Germany<sup>(11)</sup>.

6. HDL-cholesterol (HDL-C) by enzymatic colorimetric test using HDL-Cholesterol test kit from Human Gesellschaft für Biochemica und Diagnostica, Germany<sup>(12)</sup>.
7. Calculation of LDL-cholesterol (LDL-C) using the following equation:

$$LDL-C = TC - HDL-C - \frac{TG}{5} \text{ (mg/dl)}^{(12)}$$

8. Serum carnitine by enzymatic ultraviolet test using L-carnitine kit from Boehringer Mannheim, Germany<sup>(13)</sup>.

**Exercise testing** by cardiopulmonary evaluation performed in the Chest Specialized Clinic, Children's Hospital, Ain Shams University, using Med Graphics Cardio<sub>2</sub> VO<sub>2</sub>/ECG combined system. The protocol used was the Bruce walking protocol<sup>(14)</sup>. Data obtained from the exercise test were:

1. Exercise duration (minutes).
2. Ventilatory parameters including VO<sub>2</sub> max (mL/min) and RER [ratio of ventilatory CO<sub>2</sub> production/O<sub>2</sub> consumption (VCO<sub>2</sub>/VO<sub>2</sub>)].
3. Anaerobic threshold (AT) which is the VO<sub>2</sub> consumption at the end of aerobic capacity and start of anaerobic metabolism (mL/min).

All patients received carnitine sup-

plementation (Carnitene 1 gm / 5 mL ampoules supplied by Sigma Tau, Italy) by the intravenous route in a dose of 25 mg/kg thrice weekly at the end of each dialysis session for a period of 5 weeks, after which lipid profile and exercise testing were re-evaluated.

Data were analyzed with Statistica Software Package v.5 (Statsoft, Tulsa, OK, USA). All numeric data were expressed as mean ± standard deviation (SD). Data were analyzed using student t test and paired t test to compare mean values of different variables. Pearson r correlation coefficient was used to determine the relationship between different quantitative variables. For all tests a probability (p) less than 0.05 was considered significant.

## RESULTS

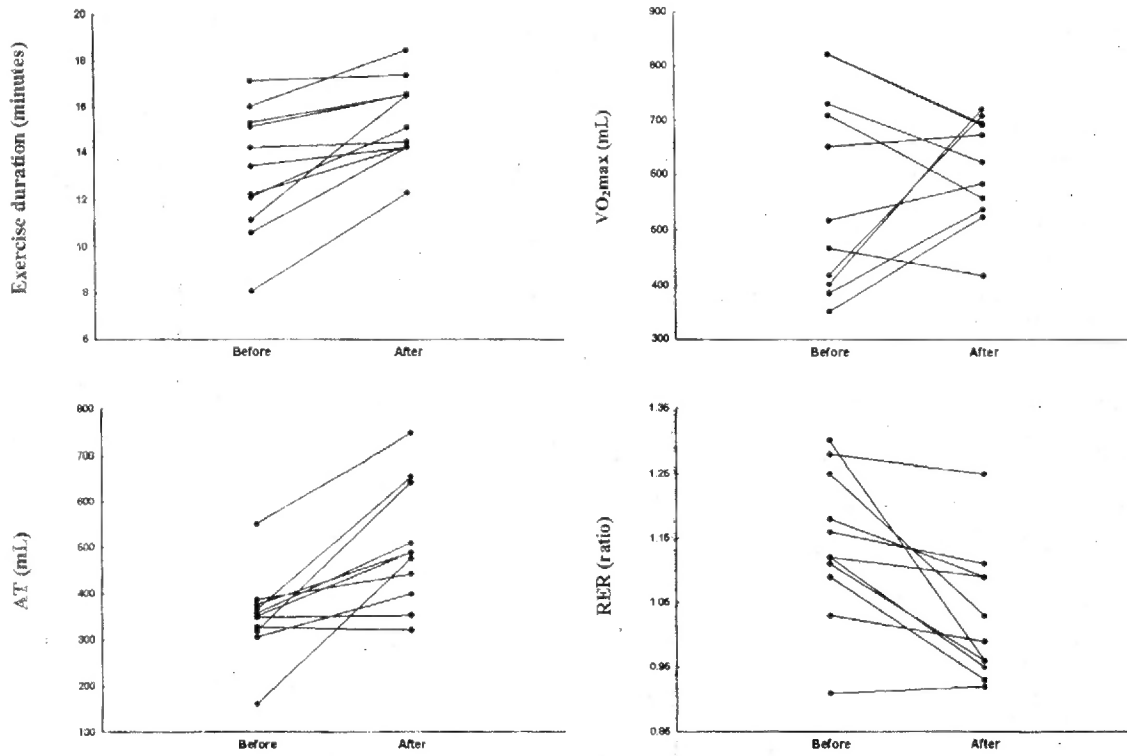
Serum carnitine was significantly lower in patients with ESRD on HD compared to controls. Supplementation of carnitine did not show any effect on lipid profile. However, carnitine therapy caused significant improvement in three of the four exercise parameters used in this study, namely exercise duration, anaerobic threshold and RER (Table 1 and Fig. 1).

A significant positive correlation between hemoglobin level and VO<sub>2</sub> max was detected in the studied patients before therapy (Fig. 2).

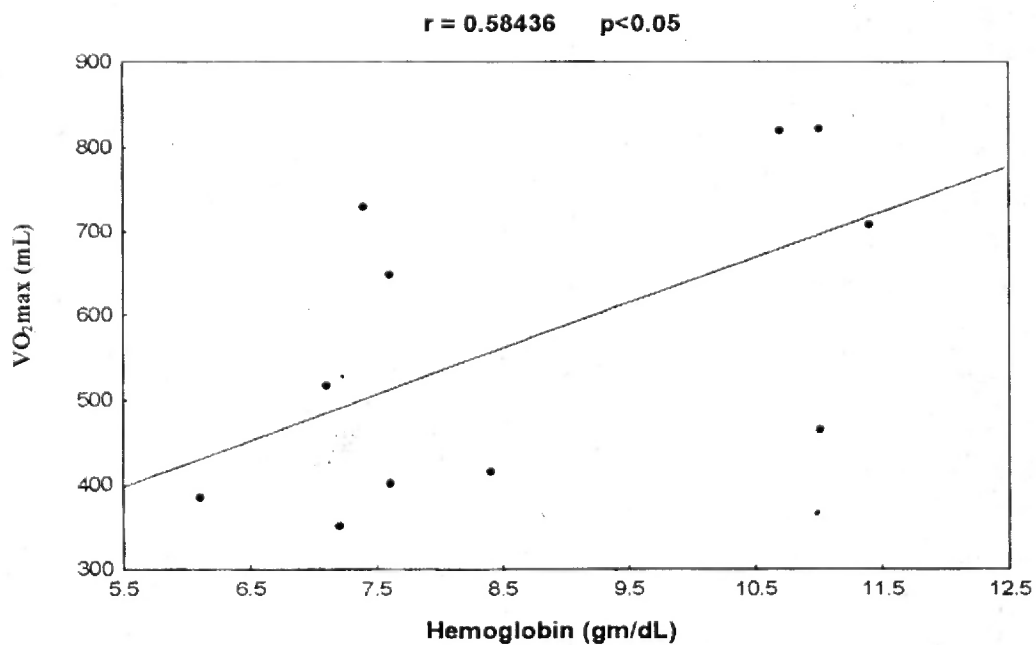
**Table 1: Comparison between control and patient groups before and after therapy for various studied parameters.**

Parameter		Control	Patients before therapy	Patients after therapy	t1	t2	t3
Laboratory parameters	Hb (gm/dL)	12.33 ± 0.97	8.68 ± 1.94		7.02*		
	BUN (mg/dL)	14.1 ± 2.26	144.45 ± 23		25.47*		
	CR (mg/dL)	0.54 ± 0.178	10.78 ± 2.2		20.98*		
	Carnitine (mg/L)	10.71 ± 1.33	3.88 ± 2.64		9.62*		
	TG (mg/dL)	60.0 ± 20.43	189.45 ± 58.78	179.81 ± 62.36	9.01*	7.94*	0.45
	HDL-C (mg/dL)	55.7 ± 16.67	37.71 ± 6.51	37.81 ± 9.91	3.41*	3.2*	0.03
	LDL-C (mg/dL)	63.38 ± 28.21	72.15 ± 35.9	74.29 ± 29.9	0.75	1.04	0.38
	TC (mg/dL)	130.6 ± 32.94	148.0 ± 32.65	148.54 ± 34.18	1.41	1.43	0.06
Exercise testing	Exercise Duration (min.)	17.28 ± 2.41	13.19 ± 2.67	15.41 ± 1.77	4.33*	2.2*	4.42*
	VO <sub>2</sub> max (ml)	1304.9 ± 740.5	570.36 ± 180	610.54 ± 95.7	3.21*	3.07*	0.77
	AT (ml)	746.2 ± 440.27	350.18 ± 90.6	562.45 ± 131.5	2.92*	1.78	4.3*
	RER (ratio)	0.95 ± 0.23	1.14 ± 0.11	1.02 ± 0.1	2.47*	0.94	3.67*

Hb = hemoglobin; BUN = blood urea nitrogen, CR = creatinine, TG = triglycerides, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, VO<sub>2</sub> max = peak ventilatory oxygen consumption, AT= anerobic threshold, t1 = comparison between control and patients before therapy, t2 = comparison between control and patients after therapy, t3 = comparison between patients before and after therapy, \* = p < 0.05.



**Fig. 1: Changes in exercise duration, VO<sub>2</sub> max, AT and RER before and after carnitine therapy in the patient's group.**



**Fig. 2: Correlation between hemoglobin level and VO<sub>2</sub> max in the studied patients before therapy.**

## DISCUSSION

Patients on HD therapy for ESRD have reduced exercise tolerance. Multiple processes related to uremia and HD have been implicated in the pathogenesis of this impairment<sup>(3)</sup>. The chronic anemia of renal failure, structural changes in the type II (fast-twitch) muscle fibers and abnormalities in skeletal muscle metabolism including impairment in fatty acid oxidation are all accused. Finally, deconditioning and underlying cardiovascular disease in many patients may limit exercise capacity<sup>(6)</sup>.

In the current study, significant exercise intolerance among patients' group in comparison to healthy controls was elicited. This was in the form of shorter exercise duration, lower peak  $VO_2$  ( $VO_2$  max), lower AT and higher RER ( $VCO_2/VO_2$  ratio). This is in agreement with Hiatt et al. (1991)<sup>(6)</sup> and Tsuyuki et al. (2003)<sup>(15)</sup>.

In addition, Ahmad et al. (1990)<sup>(16)</sup> and Sietsema et al. (2002)<sup>(3)</sup> detected significant impairment of peak  $VO_2$  among their group of ESRD patients and characterize it as an index for exercise limitation and follow up parameter for exercise training.

The negative correlation between peak  $VO_2$  and hemoglobin level among our group of patients supported the observation reported by many investigators that increasing oxygen content by treatment of anemia would increase the peak  $VO_2$ <sup>(4)</sup>.

However, Miro et al. (2002)<sup>(17)</sup> concluded from their study that persistence of abnormally low peak  $VO_2$  even after restoration of hemoglobin concentration with recombinant erythropoietin therapy and studies of muscle bioenergetics, suggests that the problem is located beyond

hemoglobin oxygen transport. AT which is the  $VO_2$  consumption at the end of aerobic capacity and start of anaerobic metabolism was also found to be significantly lower among the patients' group which pointed to a marked impairment of aerobic capacity. The same finding was detected by Hiatt et al. (1991)<sup>(6)</sup> who measured serum lactate as an index for aerobic capacity but this is considered an invasive tool. The same was recorded by Molsted et al. (2004)<sup>(18)</sup> who used different physical activities to examine the aerobic capacity but this was considered a subjective tool. In addition, Tsuyuki et al. (2003)<sup>(15)</sup> could elicit lower peak  $VO_2$ , and anaerobic threshold among their group of HD patients. They stated that peak  $VO_2$  and AT could be considered as monitoring tools for cardio-respiratory functional reserve during physical training. RER ( $VCO_2/VO_2$ ) is an important exercise and metabolic parameter that was found to be higher among our patients' group in comparison to healthy controls. This is in agreement with Hiatt et al. (1991)<sup>(6)</sup>, Tsuyuki et al. (2003)<sup>(15)</sup> and Koufaki et al. (2001)<sup>(19)</sup> documented the reproducibility of exercise testing and that it quantifies exercise intolerance. So they recommended exercise training among their patients with ESRD.

Carnitine is an important cofactor for normal cellular metabolism. Optimal utilization of fuel substrate for ATP generation by skeletal muscle during exercise is dependent on adequate carnitine stores<sup>(20)</sup>.

Patients with ESRD under conservative treatment are known to have hypercarnitine-mia due to reduction of the elimination of carnitine by the impaired kidney. However, HD patients have low plasma carnitine level

due to carnitine losses that are not compensated for by endogenous synthesis of carnitine<sup>(21)</sup>.

In the current study a significant lower serum carnitine level was elicited among patient's population versus the healthy control group. This is in agreement with many previous studies<sup>(22-24)</sup> that explained this finding not only by carnitine losses but by lacking of carnitine in diet and impairment of renal carnitine synthesis and reabsorption. It is worth mentioning that some investigators related the exercise intolerance in HD patients to the impaired carnitine availability and/or alterations in carnitine metabolism<sup>(1)</sup>. In spite of the absence of a significant correlation between carnitine level among our patients with the different exercise parameters, a statistically significant improvement of AT and RER was elicited after a complete course of carnitine therapy. Brass et al. (2001)<sup>(7)</sup> also could not elicit a significant change in peak VO<sub>2</sub> with carnitine therapy, but they found a significant improvement of the fatigue domain of the KDQ (kidney disease questionnaire) after 12 weeks of carnitine therapy.

In addition, an earlier study done by Kavukcu et al. (1998)<sup>(25)</sup> elicited significant improvement of respiratory function tests in children undergoing chronic HD after carnitine therapy as a part of improvement of exercise capacity, energy metabolism and muscle mass.

However, carnitine supplementation has been recently approved by the US Food and Drug Administration not only for the treatment, but also for the prevention of carnitine depletion in dialysis patients<sup>(5)</sup>.

In conclusion, ESRD pediatric patients on HD have significant impairment in exercise performance that can affect their style of life. VO<sub>2</sub>, AT and RER could all be considered as useful, reproducible, non-invasive ways to evaluate exercise capacity among those patients. Carnitine deficiency is considered an important contributing factor of this exercise intolerance. Because of this, carnitine therapy should be considered in rehabilitation programs for those patients to improve their physical activity, increase exercise tolerance, increase feelings of well-being and enhanced stability on dialysis.

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