

## Effect of Hemodialysis on Carnitine Levels in Children with Chronic Renal Failure

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### ABSTRACT

**Background:** Levocarnitine is a molecule required in mammalian energy metabolism. It removes the potentially toxic acyl groups from the cell helping to maintain normal metabolic functions.

**Objectives:** The aim of this work is to study serum carnitine levels in children with end stage renal failure and the effect of conservative management and regular hemodialysis on this level.

**Methods:** This study included 10 children with end stage renal disease under conservative management (4 males and 6 females), 20 children with end stage renal disease under regular hemodialysis (6 males and 14 females), and 10 apparently healthy control children (5 males and 5 females). All groups were age matched. All patients were subjected to complete history taking, thorough clinical examination and ECHO. In the third group full history of dialysis duration, number of sessions, duration of each session, size of filter used and type of filter were taken. Laboratory investigations were done including complete blood picture, blood urea, serum creatinine, sodium, potassium, calcium, phosphorous, and albumin level in serum. Serum carnitine level was done to all subjects, one sample from the control group and from patients under conservative management and three samples from patients under regular hemodialysis: predialysis, immediately postdialysis and 1 hour postdialysis.

**Results:** We found that serum level of carnitine in the healthy group was  $9.8 \pm 1.5$  mg/l, while in patients with chronic renal failure under conservative management the serum carnitine level was  $1.3 \pm 1.2$  mg/l and serum carnitine level of patients with chronic renal failure under regular hemodialysis was  $3.98 \pm 1.94$  mg/l. There was no correlation to size of filter. We found that serum carnitine level was not significantly lower with filters of polysulphone with a level of  $3.4 \pm 1.4$  mg/l, than cuprophane with a level of  $4.6 \pm 2.3$  mg/l. There was a positive correlation between serum carnitine level and duration of the disease. We found that the predialysis basal level ( $3.98 \pm 1.94$  mg/l), was highly significantly lower immediately postdialysis ( $1.35 \pm 0.94$  mg/l) and starts rising but still remained less than basal level 1 hour postdialysis ( $2.16 \pm 1.15$  mg/l).

**Conclusions:** We concluded that children with end stage renal disease have a lower serum level of carnitine than age matched healthy children. Children under conservative management may have a lower level than those on regular hemodialysis. Serum carnitine level decreased rapidly during hemodialysis and started to rise to a level near the predialysis basal level 1 hour after the hemodialysis session. So, we recommend measurement of serum carnitine level in all children with end stage renal disease either on conservative management or on regular hemodialysis to detect the deficiency as early as possible. Supplementation of patients on conservative management with iron and vitamin B complex and amino acids should be done to ensure carnitine synthesis.

### INTRODUCTION

Carnitine, gamma-trimethyl-beta-hydroxybutyrobetaine, is a small molecule widely present in all cells from prokaryotic to eukaryotic<sup>(1)</sup>. In addition, it facilitates the

transport of long-chain fatty acids across the mitochondrial membrane for beta-oxidation and subsequent energy production in skeletal muscle and myocardium. It has been shown in numerous studies that

levocarnitine metabolism is abnormal in patients with end-stage renal disease<sup>(2)</sup>. Carnitine is a conditionally essential metabolite that plays a critical role in cell physiology by participating in transesterification reactions and preventing organic acid accumulation. A number of disease states are characterized by carnitine depletion that may lead to metabolic and clinical disturbances<sup>(3)</sup>.

Impaired structural and metabolic integrity of the kidney in chronic renal failure (CRF) affects carnitine metabolism by means of many factors. Depletion due to hemodialysis (HD) is one of the major concerns. Children with CRF, either dialyzed or undialyzed, have decreased plasma free carnitine (FC) levels. Hemodialysis treatment significantly depletes plasma FC concentrations during the procedure, but predialysis levels are reached 1 hr after ceasing HD<sup>(4)</sup>. Serum carnitine levels depend on weekly dialysis time and on carnitine supplementation<sup>(5)</sup>.

Carnitine supplementation in hemodialysis patients may improve the hematological status (allowing a reduction of the requirement for erythropoietin), the exercise tolerance, the plasma lipid profile, and the intradialytic symptoms. In addition, carnitine supplementation may improve cardiac functions, protein metabolism, and insulin resistance. 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>(3)</sup>.

#### AIM OF THE WORK

The present study was undertaken to

assess the level of serum carnitine in children with end stage renal failure and to investigate the effect of conservative management and regular hemodialysis on serum L-carnitine.

#### SUBJECTS AND METHODS

This study was carried out in the Pediatric Dialysis Unit of Ain Shams University Hospitals, and the Pediatric Dialysis Unit, Zagazig University Hospitals, during the period from August 2002 to April 2003. It included 40 subjects. They were divided into 3 groups.

**Group A:-** It included 10 age matched healthy children. They were 5 males and 5 females. Their ages ranged from 8 to 16 years with a mean value of  $12.8 \pm 2.6$  years.

**Group B:-** It included 10 patients with renal insufficiency under conservative management. They were 4 males and 6 females. Their age ranged between 6 and 15 years with a mean value of  $11.6 \pm 3.4$  years.

**Inclusion criteria** were as follows: stable clinically, and duration of ESRD of at least 6 months.

**Exclusion criteria** were:- medical instability or under carnitine supplementation.

**Group C:-** It included 20 patients with ESRD under regular hemodialysis. They were 6 males and 14 females. Their age ranged between 9 and 18 years with a mean value of  $13.05 \pm 2.5$  years. Hemodialysis was performed with bicarbonate dialysate for 2.5 to 3 hours in each session. All were on three times dialysis per week. Dialyzer surface area ranged from 0.3 to 1 m<sup>2</sup>. Ten patients were on polysulfone membrane and the other 10 patients were on cuprophan type.

**Inclusion criteria** were:- stable maintenance hemodialysis, duration of dialysis at least 6 months.

**Exclusion criteria** were:- medical instability, or under carnitine supplementation.

#### **METHODS:**

**1- Full history taking** laying stress on etiology, duration of the disease, and for patients under hemodialysis duration of dialysis, number of sessions, dialyzer type and size. History of any cardiac symptoms or echocardiography results. History of erythropoietin supplementation, iron supplementation, and vitamin B complex supplementation. All patients on hemodialysis were receiving the three while no patients on conservative management were under any supplementation apart from oral iron supplementation only.

**2- Thorough clinical examination** with special stress on body weight, height, blood pressure and local heart and abdomen examination.

#### **3- Laboratory investigations**

- Kidney function tests and serum albumin were estimated using autoanalyzer Dimension RXL (Dade Behring USA).
- Serum K, Na were estimated using electrolyte-analyzer AVL988-3.
- Serum phosphorus was estimated by colorimetric methods according to Daly and Erthing Shausen<sup>(6)</sup>.
- Serum calcium was estimated by colorimetric methods according to Mundy and Guise<sup>(7)</sup>.
- Serum carnitine level was assayed by enzymatic ultraviolet test using L-carnitine kit from Boehringer Mannheim, Germany<sup>(8)</sup>.

#### **Sample collection:**

- 3 mls venous blood were drawn from each subject of group A and B.
- 6 mls of venous blood from subjects of group C: 2 ml before the dialysis session and 2 ml immediately after the session and 2 ml 1 hour after the dialysis session.

#### **L-carnitine determination by enzymatic UV test<sup>(10)</sup>:**

##### **Principle:**

L-carnitine is acetylated to acetylcarnitine by acetylcoenzyme A (ACETYL CoA) in the presence of the enzyme carnitine acetyl transferase (CAT). The resulting coenzyme A (CoA) is acetylated back to acetyl CoA in the presence of adenosine-5'-triphosphate (ATP) and acetate, catalyzed by the enzyme acetyl CoA synthetase (ACS). This results in the formation of adenosine-5'-monophosphate (AMP) and inorganic pyrophosphate (PP<sub>i</sub>). In the presence of ATP, supported by myokinase (MK) AMP forms twice the amount of adenosine-5'-diphosphate (ADP). This is converted in the following reaction with phosphoenol pyruvate (PEP) in the presence of pyruvate kinase (PK). The pyruvate formed is reduced to L-lactate by reduced nicotinamide adenine dinucleotide (NADH) in the presence of lactate dehydrogenase (LDH).

The amount of NADH consumed during the reaction is equivalent to half the amount of L carnitine. The absorption was measured at 340 nm.

#### **RESULTS**

The mean age for group A was 12.8 ± 2.6 years, 11.6 ± 3.4 years for group B and 13.05 ± 2.5 years for group C. There was no

significant difference between the groups.

As regards sex of the three groups they were: in group A, 5 males (50%) and 5 females (50%); group B, 4 males (40%) and 6 females (60%) while in group C there were 6 males (30%) and 14 females (70%).

Concerning the weight in kg, group A weight ranged between 21 and 44.7 kg with a mean value of  $32.4 \pm 7.5$  kg, group B ranged between 12.5 and 58.7 kg with a mean value of  $29.6 \pm 15.9$  kg and group C ranged between 19.75 and 51 kg with a mean value of  $31.0 \pm 8.5$  kg. There was no significant difference between the groups.

As regards height, group A ranged between 123-162 cm with a mean range of ( $145.3 \pm 13.0$  cm), group B ranged between 95-150 cm with a mean value of ( $121.6 \pm 22.2$  cm), while group C ranged between 100-150 cm with a mean value of ( $130.9 \pm 12.1$  cm), with p value of less than 0.05 which means a significant difference among groups (i.e. group B and C are significantly lower than group A).

As regards systolic blood pressure of the three groups, group A ranged between 90 and 120 mmHg with a mean value of ( $106 \pm 9.9$  mmHg), group B ranged between 95 and 130 mmHg with a mean value of ( $117.5 \pm 13.2$  mmHg), while group C ranged between 100 and 140 mmHg with a mean value of ( $113.5 \pm 14.9$  mmHg), with no significant difference among them. Concerning diastolic blood pressure, group A ranged between 55 and 75 mmHg with a mean value of ( $64.5 \pm 6.0$  mmHg), group B ranged between 55 and 90 mmHg with a mean value of ( $74.5 \pm 11.4$  mmHg) while group C ranged between 60 and 100 mmHg with a mean value ( $72.5 \pm 12.5$  mmHg),

with no significant difference between groups.

As regards duration of the disease in group B and C; duration of ESRD in group B ranged between 6 and 70 months with a mean value of ( $27.5 \pm 18.7$  months) while in group C ranged between 6 and 88 months with a mean value of ( $30.4 \pm 22.9$  months), with non significant difference between the two groups.

Blood urea values in the studied groups were as follows; group A blood urea level ranged between 10 and 23 mg/dl with a mean value of ( $16.0 \pm 4.7$  mg/dl), group B blood urea level ranged between 30 and 309 mg/dl with a mean value of ( $141.4 \pm 76.7$  mg/dl) while that of group C ranged between 94 and 215 mg/dl with a mean value of ( $148.6 \pm 30.7$  mg/dl). The p value was less than 0.05 when comparing both group B and C with group A indicating a highly significant difference. Serum creatinine level mean value and ranges revealed also a highly significant difference between group B ( $3.93 \pm 2.8$ , 0.7-8.6) and C ( $8.4 \pm 1.9$ , 5.8-12.4) when compared to group A ( $0.46 \pm 0.18$ , 0.2-0.8).

Hemoglobin level mean value and ranges revealed a highly significant difference between group B ( $9.7 \pm 2.03$ , 5.9-12.6) and C ( $9.9 \pm 1.14$ , 7.5-13.3) when compared to group A ( $12.8 \pm 0.9$ , 11.5-14.3).

In group B and group C we found that 10% only of group B had cardiomyopathy detected with ECHO study while 40% of group C had ECHO positive findings of cardiomyopathy. The affection was in the form of dilated cardiomyopathy with mitral valve affection mainly. There was no significant relation between plasma

carnitine level and cardiac affection.

**As regards carnitine level:-**

Serum carnitine levels in the studied groups are shown in Tables 1 & 2.

The correlation between serum carnitine level and different data of group B and group C were all insignificant (Table 3).

Statistical analysis of different serum carnitine levels by usage of two different

types of membranes (polysulphone and cuprophane) revealed no significant difference (Table 4).

As regards size of filter and duration of dialysis session, there was no significant difference. As regards number of sessions and duration of disease, there was positive correlation between each of them and serum carnitine level (Table 5).

**Table 1: Serum carnitine level among different groups.**

	<b>Group A X ± S (range)</b>	<b>Group B X ± S (range)</b>	<b>Group C X ± S (range)</b>	<b>f</b>	<b><sup>a</sup>p <sup>b</sup>p</b>	<b>Sig.</b>
Serum carnitine level mg/l	<sup>a</sup> 9.8 ± 1.5 (7.9-12.0)	<sup>b</sup> 1.3 ± 1 (0.1-3.3)	3.98 ± 1.94 (1.9-9.5)	67.5	< 0.001	HS

ap < 0.001 when compare control with both other groups

bp < 0.001 when compare conservative group with that on regular hemodialysis

HS = highly significant

N.B. levels in-group C were that of predialysis samples.

**Table 2: Serum carnitine level among cases on regular hemodialysis.**

	<b>Carnitine level (mg/l) X ± SD (range)</b>	<b>p</b>	<b>Significance</b>
<b>Predialysis</b>	3.98 ± 1.94 (1.9-9.5)		
<b>Immediately post-dialysis</b>	1.35 ± 0.94 (0.1-3.1)	< 0.001	HS
<b>1 hour post-dialysis</b>	2.16 ± 1.15 (0.9-5)	< 0.05	Sig

HS: highly significant

Sig: significant

**Table 3: Correlation between serum carnitine levels and different data of group B and group C.**

Data	r	p	Significance	r	p	Significance
Age	0.08	0.005	NS	0.34	0.005	NS
Weight	0.09	0.005	NS	0.15	0.005	NS
Height	-0.75	0.005	NS	0.26	0.005	NS
Blood urea	0.04	0.005	NS	0.18	0.005	NS
Hemoglobin	-0.13	0.005	NS	0.2	0.005	NS
Serum creatinine	0.37	0.005	NS	+0.18	0.005	NS

NS: non significant

r: correlation

**Table 4: Effect of both types of membrane on serum carnitine level in group C.**

Type of membrane	1 <sup>st</sup> sample	2 <sup>nd</sup> sample	3 <sup>rd</sup> sample
Polysulphone	3.4 ± 1.4 (1.9-6)	1.1 ± 0.8	1.72 ± 0.7
Cuprophane	4.56 ± 2.3 (2.1-9.5)	1.6 ± 1.0	2.61 ± 1.4
T	1.36	1.19	1.82
P	0.187	0.24	0.08
Significance	NS	NS	NS

NS: non significant

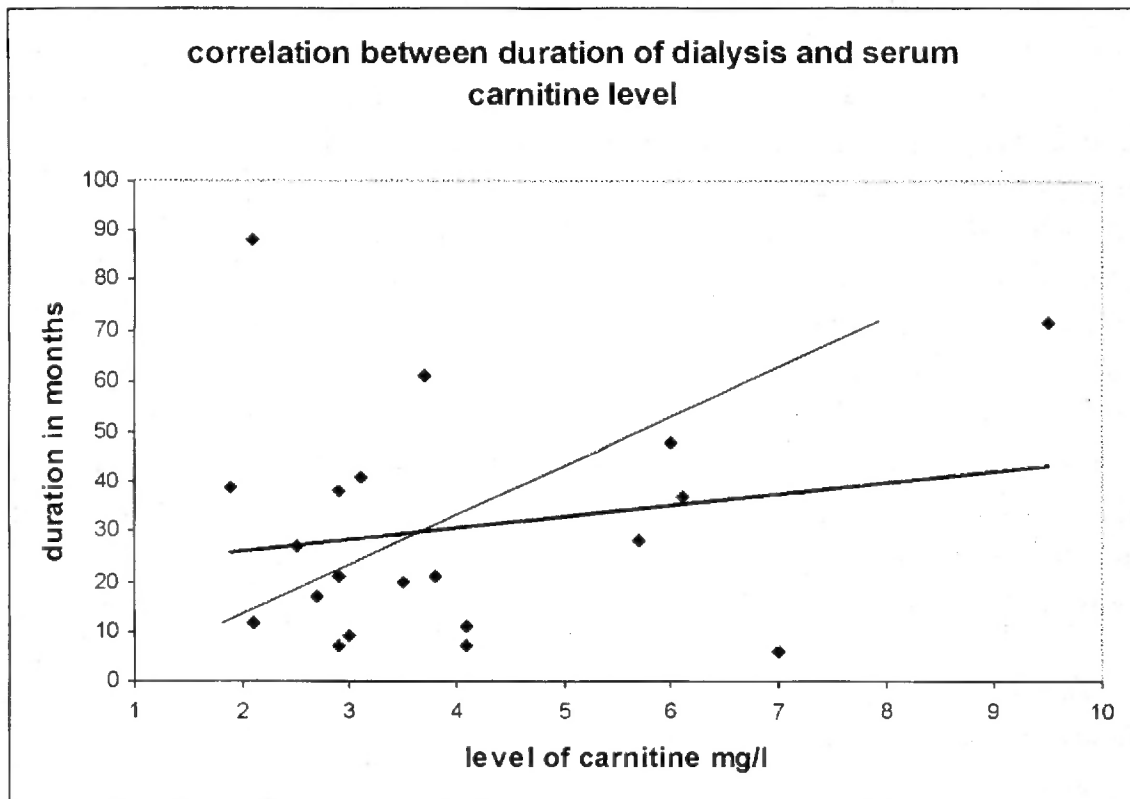
**Table 5: Some dialysis data and correlation between serum carnitine level and these parameters in group C.**

	X ± SD (Range)	r	p	Significance
Size of filter	0.79 ± 0.16 (0.3-1.0)	0.23	> 0.05	NS
Duration of dialysis session in hours	2.82 ± 0.2 (2.5-3.0)	0.2	> 0.05	NS
Number of sessions	431.55 ± 365.6 (29-1257)	0.48	< 0.01	Sig.
Duration of disease in months	30.4 ± 22.9 (6-88)	0.48	< 0.01	Sig.

Sig.= significant

NS: non significant

r: correlation



**Fig. 1: Correlation between serum carnitine level and duration of disease.**

## DISCUSSION

Levocarnitine is a molecule required in mammalian energy metabolism. It removes the potentially toxic acyl groups from the cell helping to maintain normal metabolic functions<sup>(2)</sup>. Carnitine can be manufactured in the body provided the requisite vitamins and minerals are also present. These vitamins and minerals are B1, B6, C, and iron. The amino acids lysine and methionine are also needed for carnitine synthesis<sup>(9)</sup>.

Many studies have shown that L-carnitine supplementation leads to improvements in several complications seen in uremic patients, including cardiac complications, impaired exercise and functional capacities, muscle symptoms, increased symptomatic intradialytic hypotension, and

erythropoietin-resistant anemia, normalizing the reduced carnitine palmitoyl transferase activity in red cells. In addition, carnitine supplementation may improve protein metabolism and insulin resistance. Recently, carnitine supplementation has been 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>(1)</sup>.

In this study we found a highly significant difference between serum levels of carnitine in the studied groups, since we found that the mean serum level of carnitine in the control group was  $9.8 \pm 1.5$  mg/l while in group B it was  $1.3 \pm 1.2$  mg/l and in group C was  $3.98 \pm 1.94$  mg/l. This means a highly significantly lower level of serum carnitine in patients with ESRD in

comparison to normal age matched group. This was similar to the results of Chazot et al.<sup>(10)</sup>, Matera et al.<sup>(11)</sup>, Bellinghieri et al.<sup>(1)</sup>, Mir et al.<sup>(4)</sup> and Bommer<sup>(12)</sup>. Causes of this deficiency may be due to low dietary intake of carnitine and lysine, reduced carnitine absorption in gut and loss of kidney synthesis<sup>(13)</sup>. Also, carnitine reabsorption by the kidney may be impaired<sup>(2,14)</sup>.

On the other hand Kletzmayer et al.<sup>(15)</sup>, and Rodriguez-Segade et al.<sup>(16)</sup>, observed that serum concentrations of both free and total carnitine were increased in uraemic patients compared with controls but still the ratio of free carnitine to acylcarnitine was decreased in uremic patients compared to controls.

In our study we observed that the level of serum carnitine in patients with ESRD under conservative management was significantly lower than those of ESRD under regular hemodialysis and this may be explained as follows our patients on conservative management were all either with normal urine volume or were polyuric while those on regular hemodialysis were all either oliguric or anuric and this explained larger losses of carnitine in urine in patients under conservative management than those on regular hemodialysis. None of our patients on conservative management received either intravenous iron supplementation or vitamin B complex while all our patients on regular hemodialysis received both of them and carnitine depends in its synthesis either in kidney or in liver on both elements. Also hemodialysis may be removing toxic substances from blood regularly (which may cause impairment of carnitine synthesis), while those on

conservative management did not undergo this removal of their toxins regularly as efficiently as those on regular hemodialysis. All our patients on regular hemodialysis were on bicarbonate dialysate not citrate, which affects level of carnitine much more. Citrate dialysate reduced carnitine level more as observed by Jackson and Lee<sup>(17)</sup> and Alhomida<sup>(18)</sup>.

On the other hand, Gloper et al.<sup>(14)</sup>, Wanic-Kossowska et al.<sup>(19)</sup> and Mir et al.<sup>(4)</sup> observed that children with CRF, either dialyzed or undialyzed, have decreased plasma FC levels. Also Rodriguez-Segade et al.<sup>(16)</sup> described that acylcarnitine levels of dialysed and undialysed patients were not significantly different.

In our study we also observed that in patients under regular hemodialysis the predialysis serum carnitine level was  $3.98 \pm 1.94$  mg/l and there was significant decrease immediately post dialysis (level was  $1.35 \pm 0.94$  mg/l) while post dialysis by 1 hour, level was still significantly less than the basal level ( $2.16 \pm 1.15$  mg/l). This came in agreement with Mir et al.<sup>(4)</sup>, who described that hemodialysis treatment significantly depletes plasma FC concentrations during the procedure, but predialysis levels were reached 1 hr after ceasing HD. That the predialysis level is reached in 6 hours postdialysis or more (up to 44-48 hours) was not studied in our study because of difficulty to achieve compliance of patients and also because 1 hour postdialysis samples showed that the level is increasing to near predialysis level. The decrease in level of serum carnitine immediately postdialysis may be explained by losing carnitine in dialysis as it is a micromolecule



as described by Goral<sup>(2)</sup>, who described that the small water-soluble carnitine molecule is dialyzable and a 75% decrease in plasma concentration has been noted during dialysis sessions. The increase in level of serum carnitine 1 hour postdialysis may be explained by transport of carnitine from muscle stores to the serum pool as described by Wanner and Horl<sup>(20)</sup> and Panzetta et al.<sup>(21)</sup>

In our study we found that there is a non-significant decrease in the level of carnitine in hemodialyzed patients using the polysulphone type of membrane. This came in agreement with Rodríguez-Benítez et al.<sup>(22)</sup> and Gumprecht et al.<sup>(23)</sup>

In our study we found that there is a positive correlation between decrease of carnitine level and duration of the ESRD. This also comes in agreement with Savica et al.<sup>(24)</sup>, who concluded that muscle carnitine deficiency was apparently more severe in the longer term haemodialysis patients. On the other hand, Guarnieri et al.<sup>(25)</sup>, showed no significant relation between duration of disease or hemodialysis and level of carnitine.

In our study we found that 10% of chronic renal failure patients had cardiomyopathy detected with ECHO while about 40% are affected in patients on regular hemodialysis. The cardiac affection was also described by Barry et al.<sup>(26)</sup> and Farid et al.<sup>(27)</sup>, who stated that most patients with ESRD have cardiac problems. The possible causes for these changes are pressure overload, volume overload, A.V. fistula, Na retention, acidosis, anemia, electrolyte abnormalities and uremic toxins.

There was no correlation between level of carnitine and myocardial dysfunction.

This is contrary to Romagnoli et al.<sup>(28)</sup> and Vescovo et al.<sup>(29)</sup> who described that there is a strong correlation between level of carnitine and myocardial function. This may be explained by: L-carnitine level in chronic renal failure patients is not the only factor which affects myocardial functions. There were many other factors sharing in this action. Also the studied groups were relatively small. Lastly, cardiac functions were not assessed except by one type of investigation (ECHO), which is not sufficient to assess all cardiac functions.

We can conclude that children with end stage renal disease have a definitely lower serum level of carnitine than age matched healthy children, and those children under conservative management may have a lower level than those on regular hemodialysis. Carnitine level decreased rapidly during hemodialysis and started to rise to a level near the predialysis basal level 1-hour after the hemodialysis session. Also there was a positive correlation between the serum carnitine level and duration of disease. There was no significant decrease of the level of carnitine with polysulphone membrane. So, we recommend measurement of serum carnitine level in all children with end stage renal disease while on conservative management or on regular hemodialysis to detect the deficiency as early as possible, as well as detection of tissue carnitine level in these groups. Supplementation of patients on conservative management with iron, vitamin B complex and amino acids should be done as for those on regular hemodialysis to ensure carnitine synthesis. Carnitine supplementation in patients with end stage renal disease and the

dosage and form of its supplementation should also be studied. The relation between cardiomyopathy and carnitine level in

patients with ESRD should be studied on a larger scale and with other methods of detection of cardiac functions.

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