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The Effect of Hemodialysis on the Carnitine Levels in Children With chronic Renal Failure.

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Abstract:
Background*: Carnitine is an essential intermediary in fat metabolism. It is necessary to shuttle long-chain fatty acids, in the form of acylcarnitines, into mitochondria for beta-oxidation. Also, it is crucial for energy production in tissues dependent upon fatty acid oxidation, such as cardiac and skeletal muscle.*
Aim of the study*: is to examine the effect on heamodialysis and the level of carnitine enzymes.*
Methods: *A total of 40 children, divided into 3 groups. The study was conducted at the pediatric dialysis unit of banha university hospital, during the period from May 2014 to December 2015.*
Results: *the mean serum carnitine level in the three studied groups were as follow, in group A range between 1.7to2.8 with mean value of (5.1±5.6), for group B range between 0.6 to 3.7 with mean value of (1.8±1), and for group C range between 7.9 to 12with mean value of (9.8±1.40).There is highly significant decrease immediate post dialysis with mean value of 1.6±0.9 mg/l and start in raising 1h post dialysis with mean value of 2.5±1 mg/l.*
Conclusion: *based on the findings we can conclude that serum level of carnitine decrease rapidly during hemodialysis and start to rise to a level near the predialysis basal level 1-hour after hemodialysis session.*
Recommendation: *There is no strong evidence that L-carnitine supplementation in dialysis patients improves muscle wasting or weight loss, exercise capacity, cardiomyopathy, or intradialytic symptoms, although it appears to be safe. Among dialysis patients, we recommend not administering oral L-carnitine.*
Keywords*: Carnitine, heamodialysis, children, chronic renal failure.*

I. Introduction

Worldwide, chronic kidney disease (CKD), especially end-stage renal disease (ESRD), is the most frequently health problem and main cause leading to kidney-related deaths. It currently affects approximately 40.3 million adults in 2010, and is projected to reach 54.8 million in 2020 [1]. Recently, kidney replacement therapy is the main measure to treat kidney failure, which dramatically improved patients' survival and the quality of life. It has been reported that a number of factors and co-morbid conditions common in dialysis are implicated as risk factors, including diabetes, hypertension, hyperlipidemia, inflammation, anemia and imbalances in mineral metabolism [2]. Among them, one of the most important complications of cardiovascular origin and the risk of cardiovascular disease in patients with chronic renal disease is hyperlipidemias [3].

Carnitine, gamma-trimethyl-beta-hydroxybutetaine, is a small molecule widely present in all cells from prokaryotic to eukaryotic[4].L-Carnitine is critical for the transportation of long-chain fatty acids across the inner mitochondrial membrane for subsequent β oxidation and energy production . Patients with end-stage kidney disease (ESKD) who are undergoing maintenance hemodialysis usually suffer from progressive L-carnitine deficiency; loss via dialysis is the main cause. Abnormalities in carnitine homeostasis may have profound biochemical effects on serum lipid, red blood cells, cardiac muscle, and skeletal muscle. Dialysis-related carnitine deficiency can be corrected with exogenous supplementation [5,6].

Carnitine is derived from red meat and dairy products in the diet, biosynthesis in the liver, kidney, and brain is adequate to meet normal requirements in healthy individuals. Approximately 95 percent of carnitine is stored in muscle, where it is concentrated by a specific transporter. Free carnitine is filtered at the glomerulus, and over 90 percent undergoes tubular reabsorption. By contrast, renal tubular absorption of acylcarnitine is limited, and clearance of acylcarnitine is four to eight times greater than that of free carnitine [7].

In chronic kidney dysfunction, clearance of both free carnitine and acylcarnitine is reduced. Plasma levels of free and total carnitine are unchanged, but serum acylcarnitine rises in inverse relation to the decline of the glomerular filtration rate (GFR) [8]. In hemodialysis patients, plasma total carnitine concentration is normal or elevated; the free carnitine concentration is reduced (19.2 to 32.4 micromol/L) and significantly lower than in healthy controls (40 to 50 micromol/L) or in chronic kidney disease (CKD); the acylcarnitine concentration is markedly increased, and the ratio of acyl to free carnitine (AC:FC) is markedly increased (0.77 to 0.96)

compared with healthy controls (0.15 to 0.25) [4,6].Effective carnitine deficiency exists if free carnitine is inadequate to meet metabolic needs; such carnitine deficiency further impairs fatty acid oxidation. However, the plasma carnitine profile does not predict whether effective carnitine deficiency exists. The vast majority (95 percent) of hemodialysis patients have low free plasma carnitine, but neither plasma total, free, or acylcarnitine nor their ratios predict clinical response to L-carnitine supplements [9,10].

L-carnitine supplementation increases plasma total, free, and acylcarnitine levels; the AC:FC ratio falls (improves) only moderately and incompletely, suggesting that carnitine continues to bind acyl residues that are present in excess in dialysis patients [11].The decline of free carnitine levels depends on dialysis vintage. In a study of 21 patients, plasma L-carnitine levels principally decreased within the first few months of beginning hemodialysis, while levels in muscle continued to decline, even after one year of dialysis [10]. These findings are consistent with a pharmacokinetic model of L-carnitine in patients receiving hemodialysis [12].

There are several studies supporting the sight that L-carnitine supplementation improves the plasma lipid profile, exercise capacity and oxygen utilization, muscle strength, intradialytic symptoms, sense of well-being, hospitalization rate, inflammatory markers, protein metabolism, left ventricular hypertrophy and cardiac function, anemia, and response to erythropoietin. In many of these instances, the physiologic rationale for administration of L-carnitine is appealing.

However, data evaluating these possible benefits of L-carnitine supplementation in hemodialysis patients are limited, with many trials being uncontrolled and small in size. Although some controlled prospective studies have been performed, trials have been limited by small size, inclusion of patients independent of signs and symptoms of carnitine deficiency, and relatively short follow-up [13,14].

In general, a growing literature supports benefits with L-carnitine supplementation on inflammation and muscle wasting. However, the evidence is unclear that L-carnitine supplementation in dialysis patients improves exercise capacity, cardiomyopathy, or intradialytic symptoms.

In a controlled trial, L-carnitine supplementation reduced blood urea nitrogen (BUN) and plasma concentrations of creatinine and phosphate compared with placebo and increased mid-arm muscle circumference, suggesting a decline in muscle catabolism; however, the constancy of delivered dialysis and diet was not verified [15]. Another a randomized, controlled trial showed that L-carnitine administration reduced serum amyloid A protein in dialysis patients [16].

Significant of the study

L-carnitine may improve cardiac and skeletal muscle energy metabolism, thereby possibly ameliorating intradialytic symptoms [17]. A meta-analysis done (2008) that included 193 patients found no effect of L-carnitine on intradialytic hypotension and only a tendency to ameliorate muscle cramps, which did not achieve statistical significance [18]. In addition, a randomized study that was published after the meta-analysis and included 92 hemodialysis patients showed no effect of L-carnitine supplementation on hypotensive episodes [19]. Evidence examining that carnitine supplementation improves quality of life is conflicting [20].

II. Aim Of The Study

The aim of the current study is to evaluate the effect of hemodialysis on carnitine levels among children with chronic renal failure.

III. Subjects And Methods

Setting:

The study was carried in the pediatric dialysis unit of banha university hospital, during the period from May 2014 to December 2015.

Subjects:

A total of 40 subjects, they were divided into 3 groups. Group (A) consist of 20 patients with regular hemodialysis. They were 12 female and 8 male. Group (B) consist of 10 patients with chronic renal failure under conservative management. And group (C) consist of 10 age matched healthy children. With the following Inclusion criteria as; stable clinically, stable maintenance hemodialysis duration of dialysis at least 3moths before. and duration of ESRD of atleast 4 months. While, medical instability, or under carinitine supplementation were excluded.

Work field:

For the three groups the following was done:

1-Full history taken;

Laying stress on etiology, duration of disease, for patients under hemodialysis duration of dialysis, number of session.History of erytheropoitin supplementation in dose of 150 IU /KG once weekly ,and iron supplementation also history of vitamin B complex supplementation where all patients on hemodialysis were

under all three subject ademonstration while no one of others on conservative managements were under supplementation of any of them apart from oral iron supplementation only .

2-Clinical examination;

With stress on body weight, height, bloodpressure ,and local heart and abdominal examination.

3-Laboratory investigations;

Blood urea ,serumcreatinine,serum K,Na,serum calcium and phosphate
,serumalbumin,CBC,,serum free carnitine level by Lcarnitine ELISA Kit.

Sample collection;

5ml blood of venous blood were drawn from each child of group **B** and **C** and divided into;Two ml gentely into plane tube for carnitine , allow samples to clot fortwo hours at room temperature or overnight at 4°C before centrifugationfor 15 minutes at 1000 ×g. Remove serum and assay immediately oraliquot and store samples at -20°C or -80°C.

2.Three ml of venous blood were taken in sterile tubes , for other testsFor group **A** 9 MLof blood were taken 5ml before the session of dialysis and divded into 2 ml in sterile tube for carnitine ,and 3ml in plane sterile tube for other tests ,other 2 ml was collected immediately after dialysis and other 2 ml was collected1 hour post dialysis.

Sample Preparation

Recommend to dilute the serum samples with Sample Diluent(1:400) before test. The suggested 400-fold dilution can be achieved by adding 5µl sample to 95µl of Sample Diluents. Complete the 400-fold dilution by adding 15µl of this solution to 285µl of Sample Diluents.

IV. Procedure

All reagents and samples put in room temperature before use. Centrifuge the sample again after thawing before the assay. It is recommended that all samples and standards be assayed in duplicate.Prepare all reagents, working standards, and samples as directed in the previous sections.Refer to the Assay Layout Sheet to determine the number of wells to be used and put any remaining wells and the desiccant back into the pouch and seal the ziploc, store unused wells at 4°C.Add 100µl of standard and sample per well. Cover with the adhesive strip provided.Incubate for 2 hours at 37°C. A plate layout is provided to record standards and samples assayed.Remove the liquid of each well, don't wash. In addition,add 100µl of Biotin-antibody (1x) to each well. Cover with a new adhesive strip.Incubate for 1 hour at 37°C. (Biotin-antibody (1x) mayappear cloudy. Warm up to room temperature and mix gently until solution appears uniform.Aspirate each well and wash, repeating the process two times for a total of three washes. Wash by filling each well with Wash Buffer (200µl) using a squirt bottle,multi-channel pipette, manifold dispenser, or autowasher and let it stand for 2 minutes, complete removal of liquid at each step is essential to good performance. After the last wash, remove any remaining wash Buffer by aspirating ordecanting. Invert the plate and blot it against clean paper towels.Add 100µl of HRP-avidin (1x) to each well. Cover the microtiter plate with. A new adhesivestrip. Incubate for 1 hour at 37°C .Repeat the aspiration/wash process for five times as in step 6 Add 90µl of TMB Substrate to each well.Incubate for 15-30 minutes at C. Protect from light37°C.

Add 50µl of Stop Solution to each well, gently tap the plate to ensure thorough mixing.Determine the optical density of each well within 5 minutes, using a microplate reader set to 450 nm. If wavelength correction is available, set to 540 nm or 570 nm. Subtract readings at 540 nm or 570 nm from the readings at 450 nm. This subtraction will correct for optical imperfections in the plate. Readings made directly at 450 nm without correction may be higher and less accurate.

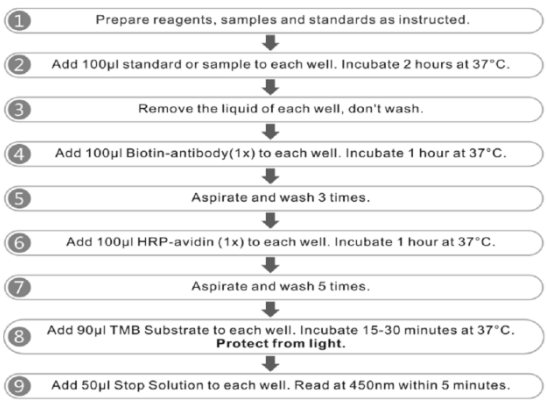

Figure (1) summary of the procedure.

V. Results

Clinical evaluation of our three groups revealed In comparison between groups as regarding age,there was no significant difference between groups as regard mean age (table1) .

Table 1: Comparison between groups as regarding age and sex

Items	**Group A (n=20)**	**Group B (n=10)**	**Group C (n=10)**	**K* test**	**P value**	**LSD**
Age (years)	13.4±2.6 (9-18 years)	0.9±**41.**10 (4-15years)	12.2±**2.4** (8—16years)	**4.4**	**0.09***	A&B
Sex	13male(65%) 7Female(35%)	5male(50%) 5female(50%)	7male(70%) 3female(30%)			

*K :kruskalwallis test
** <0.05 : significant

In comparison between groups as regarding Wt, there was no significant difference between groups as regard mean Wt .In comparison between groups asregarding Ht, there was significant difference between groups as regard mean Ht .(table 2) .

Table 2: Comparison between groups as regarding Wt. & Ht.

Items	**Group A (n=20)**	**Group B (n=10)**	**Group C (n=10)**	**T**	**P value**	**LSD**
Wt (kg)	35.5±16 (19-90kg)	29.9±**15.4** (14-57kg)	35.5±**7.9** (27-52kg)	0.567*	0.572	-----
Ht (cm)	130.5±11.7 (110-150cm)	120±19.9 (95-152cm)	141.3±**9.9** (125-162cm)	5.9**	**0.006*** **	B&C

*K test
**F test: one way ANOVA
***<0.05 significant

Comparison between systolic blood pressure of the three groups,there was no significant difference between groups as regard mean systolic blood pressure**.** Comparison between diastolic blood pressure of the three groups,there was no significant difference between groups as regard mean diastolic blood pressure**.(table3)**

Table3: Comparison between groups as regarding Bp.

Items	**Group A (n=20)**	**Group B (n=10)**	**Group C (n=10)**	**F test**	**P value**
Systolic Bp (mmhg)	117.3±13.9 (100-140)	116.5±**11.1** (100-130)	109±**9.1** (95-120)	1.6	0.2
Diastolic Bp(mmhg)	72.2±8 (60-90)	68.5±**7.8** (55-85)	68±**4.2** (60-75)	1.5	0.2

Comparison between serum **carnitine** of the three groups,there was significant difference between groups as regard mean serum carnitine in the three groups Table(4)

Table4:Distribution of the LCarnitine level in the three groups before the intervention

Carnitine serum Mg/l	**Group A (n=20)**	**Group B (n=10)**	**Group C (n=10)**	**K test**	**P value**	**LSD**
X±SD Range	**5.1±5.6 1.7-2.8**	**1.8±1 0.6-3.7**	**9.8±1.4 7.9-12**	**9.5***	**<0.001**	**A&B A&C B&C**

**U test
#<0.001: Highly significant

When compring L carnitine pre and immediate post dialysis ,there was significant difference regard mean serum carnitine in pre and immediate post dialysis .(Table5)

Table 5: L carnitine pre and immediate post dialysis

Items	Pre	Post	Welcoxon signed	P value
Carnitine Mg/l	5.1±5.6	1.6±0.99	**2.7**	**0.014(<0.05)** ***

when compring L carnitine pre and 1 hour post dialysis ,there was no significant difference regard mean serum carnitine in pre and 1 hour post dialysis .(Table 6)

Table 6:L carnitine pre and1h post dialysis

Items	Pre	1 hour post	Welcoxon signed	P value
Carnitine Mg/l	5.1±5.6	2.5±1.1	**2.08**	**0.052(>0.05)** *

when compring L carnitine immediate post and 1 hour post dialysis ,there was significant difference regard mean serum carnitine in immediate post and 1 hour post dialysis .(Table7)

Table 7: L carnitineimmediate and 1h postdialysis

Items	immediate	1h post	Wilcoxon signed	P value
Carnitine Mg/l	1.6±0.99	2.5±1.1	**10.3**	**<0.001*****

VI. Discussion

Scientific research documented that, children with end-stage renal disease (ESRD) have a shortened life expectancy compared with children without CKD. Renal transplantation remains the treatment of choice to maximize survival and growth. Approximately three-quarters of children with ESRD undergo dialysis in the United States and the mortality rate for these children is reported to be at least 30 times higher than in the general pediatric population [**21].**

The United States Renal Data System mentioned that, a decrease in mortality for children who received chronic dialysis over a 20-year period from 1990 to 2010, especially in children less than five years of age .The leading causes of death were cardiovascular disease and infection. The authors speculate that the reduction in mortality was probably due to improved predialysis care, advances in dialysis technology, and increased clinical experience in caring for these patients[**22].**

L-carnitine is well thought-out as "conditionally essential nutrient" or "conditional vitamin" which supraphysiological concentrations in plasma and target organs may exert beneficial effects on several metabolic parameters that have derangements of a common origin (e.g. insulin resistance, type 2 diabetes, dyslipidemia) and which are frequently present in end-stage renal disease patients undergoing dialysis[**23].**

In addition, L-carnitine as an essential peptide is decreased in HD patients, especially after the HD session. It is probably lost through the HD membrane during the HD session. Although it is renewed during the period between the two HD sessions, however his lack is proportional to the HD duration. This condition may cause some common dialytic symptoms that influence the morbidity and the mortality of HD patients[**24].**

In the present study, we found highly significant difference between serum levels of carnitine in the studied groups ,as we found that the mean value of serum carnitine in group c control group ranges between 7.9and12 mg/ L with mean value of 9.8±1.4 mg/L while in group B which is ESRD on conservative management was ranges between 0.6-3.7 mg/Lwith mean value of 1.8±1 mg/L and in group A which is ESRD with regular HD was ranging between1.7-2.8mg/L with mean value of 5.1±5.6.This mean that a highly significant lower level of serum carnitine in patient with ESRD on regular hemodialysis comparison to normal age matched group.This wasin the same line with [25].

The most important causes of this deficiency may be due to the following factors; Loss of renal parenchyma removes a source of endogenous carnitine synthesis.Low dietary intake of meat and dairy products deprives patients of a rich source of carnitine. Hemodialysis removes free carnitine and acylcarnitine. Although total dialytic removal is probably comparable to normal urinary excretion, free carnitine clearance by hemodialysis is greater than that of acylcarnitine. This pattern is the reverse of normal urinary carnitine excretion. Fatty acid metabolism is impaired in renal failure. Thus, incompletely metabolized acyl residues accumulate and drive the formation of acylcarnitine esters[26].

In our present study we observe 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 by ;Our patient on conservative management were all either with normal urine volume or were polyuric while those on regular hmodialysis were all either oliguric or anuria and this explained larger losses of carnitine in urine in patients under conservative management than those on regular hemodialysis as carnitine excretion is mainly through urine[27].

In the present study None of our patient on conservative management receive either intravenous iron supplementation or vitamin B complex while all our patients on regular hemodialysis receive both of them and as carnitine depends in its synthesis either in kidney or in the liver in both elements as catalysts in reaction that combine methionine and lysine to form γ-butyrobetaine as a precursor of carnitine. In addition, its synthesis in patients receiving those supplementation will be much more better than those not receiving eitheriron or

vitamin B complex specially because those patients with ESRD have generalized malnutrion as observed by so many studies [28,29].

In the present study,all patients on regular hemodialysis are on bicarbonate dialsate not under citrate type which affect level of carnitine much more i.e.bicarbonatedislate act as a preservative factor against reduction of serum carnitine level and citrate dialsatereuce level more as observed by Jakson and Lee [30] who describe that hemodialysis may therefore represent an acute period of relative carnitine deficiency when regeneration of free co enzyme fromacetyle coenzyme A consequent to metabolism of acetate .

The present study showed significantly lower level of carnitine in patients under conservative management than those on regular hemodialysis come in contrary with Mir etal[31] who found that children with CRF ,either dialyzed or undialyzed , have decreased plasma FC levels.Hemodialysis treatment significantly depletes plasma FCconcentrationduring the procedure .And our result inrelation between level of carnitine between those of ESRD under conservative treatment and those under regular hemodialysis. Also this was describe by Wanic-Kossowska and his colleges [32],who supposed that in HD patient‘s serumlevel of carnitine was significantly lower as compared to the control group of healthy subjects and to the non dialyzed patients.
In the present study we also observe that patients on hemodialysis the pre dialysis carnitine level was with mean value of 5.1±5.6 and immediate post dialysis with mean value of 1.6±0.99 with statistical significant differences. Moreover, whencomparing L carnitine pre with mean value of 5.1±5.6 and1h post dialysis with mean value of 2.5±1.1and p value showing (>0.05) not significant. Also, when comparing L carnitine immediate with mean value of 1.6±0.99and1h post dialysis with mean value of 2.5±1.1and p value showing(<0.001) with highly statistical significant. This may be due to immediate post dialysis level is very low and starting to increase after that as shown after one hour. This come with the same line with Miretal.,[32] who stated that hemodialysis significantly depletes plasma FC concentration during the procedure,but pre dialysis level reached 1 hour after ceasing HD.

Several studies have shown that supplementation of L-carnitine is a treatment of choice in HD patients, particularly for those who are resistant to erytropoetin therapy, those who suffer from lipid disturbances, intradyalitic symptoms of cramps, hypotension, etc. A study done by Kramer et al. [33] ,patients with cardiovascular disease, defined as hospitalizations for angina, myocardial infarction, arrhythmia, congestive heart failure, cerebral vascular disease or peripheral vascular disease prior to receiving carnitine, and those with anemia and hypoalbuminemia derived the greatest benefit from carnitine therapy.

A study done byWanic-Kossowska et al., [32] the influence of combined therapy with L-carnitine and erythropoietin on selected blood morphology parameters in patients treated with HD was analyzed. They realized that combined therapy could decrease the requirement for exogenous erythropoietin. The correlation between serum carnitine concentration and erythrocyte osmotic resistance indicates indirectly the beneficial effect of L-carnitine administration on erythrocyte cell membrane stabilization.[32]

VII. Conclusion And Recommendation

Base on the present findings we conclude that;Children with end stage renal disease have a definite lower serum level of carnitine than age matched healthy children. Those children under conservative management may have a lower level than those on regular hemodialysis. We can conclude that serum carnitine level decrease rapidly during hemodialysis and start to rise to a level near the predialysis basal level 1-hour after hemodialysis session.

Base on the present findings we recommended that;

1- There is no strong evidence that L-carnitine supplementation in dialysis patients improves muscle wasting or weight loss, exercise capacity, cardiomyopathy, or intradialytic symptoms, although it appears to be safe. Among dialysis patients, we recommend not administering oral L-carnitine.
2- Replicate the study with large sample size to generalize the findings.
3- Further research needed to determine cranitine level in patient on conservative management of end stage renal disease.
4- Measurement of serum carnitine level in all children with end stage renal disease while on conservative treatment or on regular hemodialysis to detect the deficiency as early as possible and detection of tissue carnitine level in the three groups.

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