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Original Article

Cardiac and Parathyroid Functions in Children on Regular Hemodialysis Treatment

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ABSTRACT

Background: Cardiovascular diseases are the major cause of mortality in uremic patients treated by hemodialysis. Left ventricular dysfunction is considered a major risk factor. It has been shown that elevated plasma phosphate, calcium-phosphate product and parathyroid hormone (PTH) are associated with an increased incidence of cardiovascular calcification and cardiovascular disease.

Objectives: This study investigated the parathyroid gland function in relation to the degree of uremia and anemia. It also aimed at detecting cardiac abnormalities in children with end-stage renal disease (ESRD) after initiation of dialysis especially left ventricular function.

Methods: The present study included 25 children with ESRD who were on regular hemodialysis treatment. Their age ranged from four to 18 years. All children were subjected to thorough history taking and clinical examination, laboratory assessment in the form of: complete blood count, serum iron, total iron binding capacity, serum ferritin, pre- and post-dialysis kidney function tests, parathyroid hormone level, pre- and post-dialysis total calcium and pre- and post-dialysis echocardiography for assessment of systolic and diastolic functions of the left ventricle.

Results: The level of PTH was elevated in 44%. There was significant intradialytic change in E/A ratio (the ratio of transmitral early diastolic flow to late atrial systole) indicating left ventricular diastolic impairment. Left ventricular myocardial performance index (LVMPI) was prolonged in 56% and there was significant correlation between PTH and LVMPI ($p = 0.03$) confirming the fact that the secondary hyperparathyroidism and the disturbances of calcium-phosphorus metabolism contribute to left ventricular hypertrophy and impaired left ventricular function.

Conclusions: Children with uremia exhibit cardiac abnormalities that may contribute to increased morbidity and mortality. These abnormalities are related to secondary hyperparathyroidism that frequently occurs in chronic renal failure.

INTRODUCTION

Chronic renal failure (CRF) is a functional diagnosis that is present when sufficient nephrons have been destroyed so that the glomerular filtration rate (GFR) is depressed with subsequent irreversible progression to end stage renal disease[1]. The management of children with CRF requires a team of pediatric nephrologists, a clinical nursing specialist, a nutritionist, a social worker and a psychologist. As renal failure, progresses to end stage renal disease (ESRD) Dialysis and transplantation staff must be included[2].

Cardiovascular disease is an important cause of mortality in patients undergoing maintenance hemodialysis accounting for almost 50% of deaths, and it is an important cause of morbidity[3]. Progressive myocardial dysfunction, as suggested by increasing left ventricular enlargement, was most pronounced within the first year of initiation

of dialysis[4]. Studies have also documented abnormal left ventricular diastolic function in patients with ESRD[5]. A number of factors may alter dynamics in renal failure including anemia, hypertension, volume overload, electrolyte imbalance, acidosis and arteriovenous fistulas[6].

The recent recognition that hyperphosphatemia, hypercalcemia and hyperparathyroidism are strong predictors of survival for patients on regular dialysis has rekindled interest in their regulation and control. These factors are associated with an increased incidence of cardiovascular calcification and cardiovascular disease in uremic patients[7].

AIM OF THE WORK

This study investigated parathyroid gland function in relation to the degree of uremia and anemia. This study also aimed at detecting cardiac abnormalities in children with ESRD after initiation of dialysis especially left ventricular function.

PATIENTS AND METHODS

The present study included 25 children, four to 18 years of age, with ESRD on regular hemodialysis treatment recruited from the hemodialysis unit of the Center of Renal Disease and Transplantation in Children, Cairo University Children Hospital.

Inclusion criteria were: 1- Age four to 18 years of both sexes. 2- On regular hemodialysis for more than 3 months. 3- Receiving at least 3 sessions per week and 4- On human recombinant erythropoietin (rh-EPO) and I.V. iron therapy.

Exclusion criteria were: 1- Age less than four years and more than 18 years. 2- Less than 3 months duration on hemodialysis. 3- Presence of congenital or rheumatic heart disease and 4- Evidence of infection or ongoing inflammatory process.

All patients were subjected to the following: thorough history taking and clinical examination, complete blood count, serum iron, total iron binding capacity, serum ferritin, pre- and post-dialysis kidney function tests, parathyroid hormone level, pre- and post-dialysis total calcium and pre- and post-dialysis echocardiography for assessment of the systolic and diastolic functions of the left ventricle.

Assessment of parathyroid hormone (PTH) was performed by drawing 3 ml of blood, centrifugation for 15 minutes at 2000-x g within 30 minutes of collection and storage of the serum at -20°C. Assay was performed using IMMULITE™ test package according to the manufacturer's specification.

A single experienced observer performed the echocardiograms (two dimensional and M mode) using HP machine (Sono® 550). M mode was used to measure left atrial diameter (LA), aortic root dimensions (Ao), LA/Ao ratio, left ventricular end diastolic diameter (LVEDD) and end systolic diameter (LVESD). The pulsed sample at the tip of the mitral valve. A minimum of three consecutive beats were analyzed, peak "E" and "A" waves were averaged ("E" is the early diastolic left ventricular wave while "A" is the left atrial systolic wave), and the E/A ratio was calculated. Global left ventricular function was calculated using the myocardial performance index (MPI or Tei index). $MPI = a - b / b$ where "a" is the time from closure to opening of the A/V

valve while "b" is the ejection time of the ventricle. In normal children, the published left ventricular MPI was 0.35 ± 0.03[8].

Data were analyzed using the Statistical Package for Social Science (SPSS) version 11. The following methods were employed: frequency distributions, percentage distributions, range, mean ± standard deviation, correlation factors (r), p values less than 0.05 were considered significant.

RESULTS

The age of the studied patients ranged from 4 to 18 years with a mean value of 12.2 ± 2 years; 16 were males and 9 were females. Duration of dialysis ranged from 0.42 to 2.5 months with a mean value of 1.5 ± 0.6 months.

Renal anemia was evident in the studied patients; mean hemoglobin level was 9.4 ± 1.8 g/dl (Table 1).

All studied patients (100%) were receiving long-term iron therapy (Table 2).

All studied patients (100%) were receiving intravenous erythropoietin therapy; mean intake was 170 ± 74 international units/kg/week (Table 3).

Fourteen cases (56%) had normal PTH levels while 11 cases (44%) had elevated PTH levels. No significant changes were observed in total serum calcium before and after dialysis ($p = 0.09$) (Table 4).

There were significant changes in the left atrial dimension (LA), left ventricular end diastolic dimension (LVEDD) and E/A ratio before and after dialysis ($p < 0.05$) (Table 5).

There were no significant changes in LVMPI before dialysis and after dialysis ($p > 0.05$). LVMPI was prolonged in 14 cases (56%). LVMPI was below normal in eight cases (32%) which increased to 10 cases post-dialysis (40%) (Fig. 1).

There were significant positive correlations between PTH and erythropoietin intake, serum ferritin and both dialysis duration and hemoglobin ($p < 0.05$) (Table 6).

A significant negative correlation was demonstrated between post dialysis serum calcium and left ventricular end diastolic dimension ($p < 0.01$). Parathyroid hormone was significantly positively correlated with pulmonary artery pressure ($p < 0.01$) and negatively correlated with left ventricular myocardial performance index ($p < 0.05$). Hemoglobin was significantly negatively correlated with left ventricular end systolic volume ($p < 0.05$) (Table 7).

Table 1: Hemoglobin levels in the studied cases.

Item	Values
Hemoglobin (g/dl)	
range	7.2 – 10.1
mean ± SD	9.4 ± 1.8

Table 2: Iron indices in the studied cases.

Item	Values
Serum iron (mg/dl)	
range	39 - 396
mean ± SD	152 ± 76
Total serum binding capacity (mg/dl)	
range	171 - 572
mean ± SD	310 ± 97
Serum ferritin (microgram/dl)	
range	247 - 2493
mean ± SD	1244 ± 616

Table 3: Erythropoietin intake in the studied cases.

Item	Values
Erythropoietin (EPO) intake (international unit/kg/week)	
range	43.5 – 322.6
mean ± SD	170 ± 74

Table 4: Calcium and parathyroid levels in studied cases.

Item	Values
Serum parathyroid hormone (PTH) level (picogram/ml)	
range	4.5 – 1040
mean ± SD	189.53 ± 273.9
Pre-dialysis total serum calcium (millimol/L)*	
range	0.82 – 1.4
mean ± SD	1.08 ± 0.17
Post-dialysis total serum calcium (millimol/L)*	
range	1.02 – 1.32
mean ± SD	1.14 ± 0.07

* p = 0.09 (non-significant)

Table 5: Mean values of pre- and post-dialysis left ventricular functions and systolic pulmonary artery pressure in studied cases.

Parameter	Pre-dialysis	Post-dialysis	p value
AO (mm)	2.08	2.22	> 0.05
LA (mm)	2.76	2.54	**< 0.05***
LA/AO	1.33	1.18	> 0.05
LVS (mm)	0.86	0.87	> 0.05
LVPW (mm)	0.79	0.77	> 0.05
LVEDD (mm)	4.2	3.98	**< 0.05***
LVESD (mm)	2.61	2.65	> 0.05
FS %	37.24	38.2	> 0.05
E/A ratio	1.24	1.4	**< 0.05***
LVMPI	0.38	0.4	> 0.05
PAP (mmHg)	34.16	34.1	> 0.05

* $p < 0.05$ (significant)

AO: aorta, LA: left atrium, LA/AO: left atrium/aorta ratio, LVS: left ventricular septum, LVPW: left ventricular posterior wall, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, FS: fraction shortening, E/A ratio: E wave / A wave ratio, LVMPI: left ventricular myocardial performance index, PAP: pulmonary artery pressure.

Table 6: Correlation coefficients (r) between laboratory data.

	Calcium (pre)	*Calcium (post)*	*PTH*	*Dialysis duration*	*Erythropoietin /kg/week*	*Hemoglobin*	*Ferritin*
Calcium (pre)							
Calcium (post)	0.31						
PTH	0.06	-0.25					
Dialysis duration	-0.01	-0.18	0.27				
Erythropoietin/ kg/week	-0.26	-0.20	**0.49***	-0.14			
Hemoglobin	0.18	-0.05	0.18	0.40	-0.27		
Ferritin	-0.13	-0.29	0.27	**0.47***	0.27	**0.48***	

* $p < 0.05$ (significant)

Table 7: Correlation coefficients (r) between laboratory data and echocardiographic data.

	Calcium (pre)	*Calcium (post)*	*PTH*	*Erythropoietin /kg/week*	*Hemoglobin*
PAP (mmHg)	-0.05	-0.36	**0.76****	0.33	-0.07
LVMPI	-0.17	-0.07	**-0.43***	0.29	0.18
E/A ratio	-0.22	0.11	0.11	0.07	-0.32
AO (mm)	-0.07	-0.28	0.31	0.04	-0.04
LA (mm)	0.07	-0.23	0.39	-0.001	-0.14
LVS (mm)	0.16	-0.16	0.32	-0.06	-0.11
LVPW (mm)	0.07	-0.09	0.30	-0.04	-0.19
LVEDD (mm)	-0.16	**-0.51****	0.18	-0.19	-0.25
LVESD (mm)	-0.21	-0.34	0.01	-0.01	**-0.47***
FS%	0.02	0.23	0.02	0.05	0.14

* $p < 0.05$ (significant) ** $p < 0.01$ (highly significant)

AO: aorta, LA: left atrium, LVS: left ventricular septum, LVPW: left ventricular posterior wall, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, FS: fraction shortening, E/A ratio: E wave / A wave ratio, LVMPI: left ventricular myocardial performance index, PAP: pulmonary artery pressure.

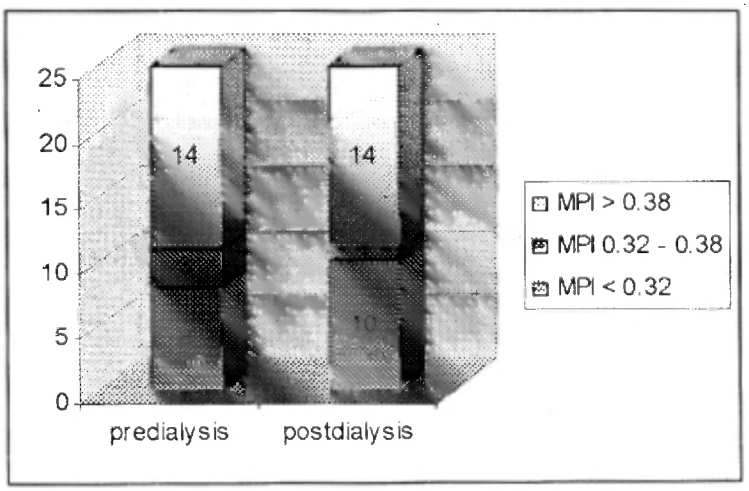

Fig. 1: Left ventricular myocardial performance index (LVMPI) pre- and post-dialysis in cases.

DISCUSSION

Elevated plasma calcium, phosphate and PTH are associated with an increased incidence of cardiovascular diseases in patients with chronic renal disease that lead to increased mortality among those patients[9]. This study aimed at detecting cardiac abnormality in children with ESRD after initiation of dialysis especially the left ventricular function using the myocardial performance index (MPI or Tei index) and correlating it with the parathyroid hormone level.

The present study included 25 children with a mean age of 12 ± 2 years, and a mean duration of dialysis of 1.5 ± 0.6 months. The mean value of pre-dialysis serum calcium was 1.08 ± 0.17 mmol/L, which increased to 1.14 ± 0.07 after the dialysis session. This is explained by the calcium concentration in the dialysate solution (1.5 to 1.8 mmol/L). However, these changes did not reach a significant level ($p = 0.09$). Parathyroid hormone (PTH) level was normal in 14 cases (56%) and was elevated in 11 cases (44%). Nasri and colleagues (2004)[10] stated that secondary hyperparathyroidism starts during the early stages of chronic renal failure. Rix and colleagues (1999)[11] studied 218 uremic patients and found that 69% of them had secondary hyperparathyroidism. In the present study a positive correlation existed between PTH and erythropoietin ($p = 0.01$). Druek and Eckardt (2002)[12] explained this by the hyperfunction of parathyroid gland contributing to the severity of anemia in uremic patients and diminishing erythropoietin responsiveness.

The patients included in the present study received routine iron supplementation during hemodialysis. This explains the positive correlation between serum ferritin and the duration of dialysis and the correlation between serum ferritin and the hemoglobin level.

There was no significant change in the left myocardial performance index (LVMPI) before dialysis and after dialysis ($p > 0.05$). However, LVMPI was prolonged in 14 cases (56%) and this index correlated significantly with serum PTH ($p = 0.03$) confirming the fact that secondary hyperparathyroidism and the disturbed calcium-phosphorus metabolism contribute to left ventricular hypertrophy and impaired function (Virtanen et al., 1998)[13]. LVMPI was below normal in 8 cases (32%) which increased to 10 cases post-dialysis (40%). The low LVMPI in the restrictive group compared to the impaired relaxation group could be related to shortened isovolumetric relaxation time. The researchers postulate that the shortened isovolumetric relaxation time may reflect a diminished left ventricular compliance, which result in earlier opening of mitral valve in diastole, and thus shortening of the left isovolumetric relaxation time.

Huting (1991)[14] stated that the ventricular diastolic function is abnormal in cases with ESRD based on peak flow velocity measurements in the early filling phase of diastole (E) and the late filling phase due to atrial systole (A). Typically the E wave velocity is decreased and the A wave velocity is increased, so the E/A ratio is decreased. This correlates with the results in the present study where the mean pre-dialysis E/A ratio was 1.24 which increased

post-dialysis to 1.4 ($p < 0.05$). Normally the mean E/A ratio is equal 2.2 ± 0.7[15]. Myocardial performance index conceptually combines both systolic and diastolic functions and is not affected by tachycardia commonly observed in young children. This is in contrast to the E/A ratio, which is difficult to obtain in tachycardia, and is affected by respiration and mitral regurgitation (Genjyu et al., 1999)[16].

There were also significant intradialytic changes in LVEDD (mean value of 4.2 mm pre-dialysis, reduced to mean value of 3.9 mm post-dialysis, < 0.05). This was also found in the LA dimension (pre-dialysis mean = 2.7 mm while post-dialysis mean = 2.5 mm, $p < 0.05$). These changes reflect a state of dilatation in the left atrium and left ventricle due to volume overload in the pre-dialysis phase, which decreases significantly in the post-dialysis phase.

A highly significant negative correlation was found between LVEDD and post-dialysis serum calcium ($p < 0.01$), indicating that low serum calcium was associated with left ventricular dilatation. Dreuke and Rostand (1999)[9] postulated that hyperparathyroidism in chronic renal failure contributed to an increase in the prevalence of cardiovascular disease and hypertension.

Hyperparathyroidism has an important role in the pathogenesis of uremic cardiomyopathy (Avram et al., 2001)[17]. The highly significant correlation between PTH and PAP ($p < 0.01$) reflects a positive relation for the increase in PAP by hyperparathyroidism in uremia, which develops in face of a workload (Lee et al. 2002)[18]. PTH positively correlated with LVMPI ($p < 0.05$) reflecting that secondary hyperparathyroidism attributed to left ventricular hypertrophy and impaired left ventricular function in uremic patients. We found no correlation between PTH and indices of diastolic function. This is explained by the fact that all our cases received vitamin D therapy for long periods, which prevented the deleterious effects of hyperparathyroidism on myocardial function.

A significant negative correlation was demonstrated between LVESD and hemoglobin level ($p < 0.05$) supporting the fact that dilatation is related at least in part to anemia. Left ventricular dilatation may represent an initial compensatory state before the ventricular hypertrophy develops as a consequence of anemia and uremia. The present study did not show significant correlation between administration of erythropoietin and different echocardiological parameters. However, Iannetti and colleagues (2000)[19] assessed the effect of therapy with erythropoietin on cardiac morphology and function in adult dialyzed patients, and found that left ventricular hypertrophy decreased significantly following long-term administration of erythropoietin. They concluded that partial correction of renal anemia with erythropoietin seems to improve cardiac performance and induces a regression in left ventricular hypertrophy.

In conclusion, children with uremia exhibit cardiac abnormalities that lead to increased morbidity and mortality. Secondary hyperparathyroidism is a main contributing factor. Therefore, routine measurement of serum PTH, calcium and phosphorus is important for early detection and

management of hyperparathyroidism. It is also important that periodic echocardiographic evaluation be an integral part of the management protocol of uremic children. The myocardial performance index (MPI) offers an easy, reliable estimate of both systolic and diastolic functions of the heart and it is recommended that it be performed for every child with chronic renal failure.

REFERENCES

1. **Massry, S. and Smogorzewski, M. (2005):** The effects of serum calcium and parathyroid hormone and the interaction between them on blood pressure in normal subjects and in patients with chronic kidney failure. J. Ren. Nutr.; 15 (1): 173-7.
2. **Rasic, S.; Kulenovic, I.; Haracic, A. and Catovic, A. (2004):** Left ventricular hypertrophy and risk factors for its development in uremic patients Bosn. J. Basic Med. Sci.; 4 (1): 34-40.
3. **Zoccali, C.; Benedetto, F.; Mallamaci, F.; Tripepi, G.; Giacone, G.; Stancanelli, B. et al. (2004):** Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. Kidney Int.; 2004 Apr; 65 (4): 1492-8.
4. **Foly, R.; Parfery, P. and Kent, G. (1998):** Long-term evolution of cardiomyopathy in dialysis patients. Kidney Int.; 54: 1720.
5. **Wanic-Kossowska, M.; Lehmann, P. and Czekalski, S. (2003):** Left ventricular systolic and diastolic dysfunction in patients with chronic renal failure treated with hemodialysis. Pol. Arch. Med. Wewn.; 109 (4): 365-73.
6. **Silverberg, D.; Wexler, D.; Blum, M. and Tchebiner, J. (2002):** The correction of anemia in severe resistant heart failure with erythropoietin and intravenous iron prevents the progression of both the heart and renal failure and markedly reduces hospitalization. Clin. Nephrol.; 50 (suppl 1): 537-45.
7. **Ritz, E. and Gross, M. (2005):** Hyperphosphatemia in renal failure. Blood Purif.; 23 (1): 6-9.
8. **Benjamin, W.; Eidem, M.; Patrick, W. et al. (1998):** Non-geometric quantitative assessment of right and left ventricular function: MPI in normal children and children with Ebstein anomaly. J. Am. Soc. Echocardiography; 11 (9): 168-79.
9. **Drueke, T. and Rostand, S. (1999):** Parathyroid hormone, vitamin D and cardiovascular disease in chronic renal failure in Nephrology Research and Training Center, University of Alabama, USA, Strostand NRTC; 56 (2): 383-92.
10. **Nasri, H.; Baradaran, A. and Naderi, A. (2004):** Close association between parathyroid hormone and left ventricular function and structure in end-stage renal failure patients under maintenance hemodialysis. Acta Med. Austriaca; 31 (3): 67-72.
11. **Rix, M.; Andersen, H.; Eskidsen, P.; Langdahl, B. and Olgard, K. (1999):** Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure. Kidney International; 56: 1084-93.
12. **Drueke, T. and Eckardt, K. (2002):** Role of secondary hyperparathyroidism in erythropoietin resistance of chronic renal failure patients. Fr. Nephrol. Dial. Transplant.; 17 (suppl 5): 28-31.
13. **Vertanin, H.; Mahdavi, H.; Kuizon, B.; El Ashoff, R. and Salusky, I. (1998):** Effect of intravenous calcitriol on cardiac systolic and diastolic function in patients on hemodialysis. Am. J. Nephrol.; 18 (5): 404-10.
14. **Huting, J. (1991):** Abnormal diastolic left ventricular filling by pulsed Doppler echocardiography in patients on continuous ambulatory peritoneal dialysis. Clin. Nephrol.; 36: 21-28.
15. **Kim, W.; Otsuji, Y.; Seward, J. and Tei, C. (1999):** Left ventricular function in right ventricular volume and pressure overload. Detection of early left ventricular dysfunction by Tei index. Jap. Heart; 40 (2): 45-54.
16. **Genjyu, E.; Masahiro, I. and Tei, C. (1999):** Assessment of global left ventricular function in normal children and in children with dilated cardiomyopathy. J. Am. Soc. Echocard.; 12 (12): 830-42.
17. **Avram, M.; Mittman, N.; Myint, M. and Fein, P. (2001):** Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. Am. J. Kidney Dis.; 38 (6): 1351-7.
18. **Lee, D.; Kim, Y.; An, S.; Jung, Y.; Kwak, L.; Shin, Y. and Rha, H. (2002):** The changes in cardiac dimensions and function in patients with end stage renal disease undergoing hemodialysis, Korean J. Intern. Med.; 17 (2): 107-13.
19. **Iannetti, E.; Carpinteri, G.; Vitale, M.; Squatrito, R.; Catalano, D. and Trovato, G. (2000):** Hyperthyroidism, therapy with erythropoietin, malnutrition and systolic function in hemodialysis: echocardiography study. Recenti. Prog. Med.; 91 (12): 632-5.