FREQUENCY AND PATTERN OF DYSLIPIDEMIA IN CHILDREN WITH END STAGE RENAL DISEASE

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ABSTRACT

Objective: To determine the frequency and pattern of dyslipidemia in pediatric patients with end stage renal disease presenting in a tertiary care hospital.

Study Design: Cross-sectional, observational study.

Place and Duration of Study: The Children's hospital and the Institute of Child Health Lahore, from Sep 2016 to Nov 2017.

Material and Methods: Children aged 5-15 years, of either gender and diagnosed with end stage renal disease were selected for the study. All the patients were undergoing renal replacement therapy in the form of hemodialysis and/or continuous ambulatory peritoneal dialysis. The serum levels of total cholesterol, triglycerides, high density lipoprotein, low density lipoprotein and very low density lipoprotein were measured.

Results: There were 138 patients in the study with mean age 11.24 ± 2.37 years and male to female ratio 2.5:1. The mean ± SD values of total serum cholesterol, triglycerides, and low density lipoprotein were found to be 174.0 ± 54.1, 241.2 ± 142.4 and 95.2 ± 49.0 mg/dl respectively. The frequency of abnormally high levels of total serum cholesterol, triglycerides, and low density lipoprotein were found to be 21.7%, 84.8% and 19.6% respectively. The lipid profile of patients on peritoneal dialysis was markedly elevated as compared to that of patients on maintenance hemodialysis (p-value ≤0.05).

Conclusion: Majority of pediatric patients with end stage renal disease had suffered from dyslipidemia especially raised serum triglycerides. Timely identification of abnormal lipid levels and appropriate management is expected to help reduce cardiovascular morbidity and mortality associated with dyslipidemia in these pediatric patients. Moreover, lipid profile of patients on peritoneal dialysis was more deranged than those on hemodialysis.

Keywords: Chronic kidney disease, Dyslipidemia, End stage renal disease.

INTRODUCTION

Chronic kidney disease (CKD) is associated with an exceptionally high burden of atherosclerotic cardiovascular disease[1,2]. According to the American Heart Association pediatric consensus guidelines, dyslipidemia is reported in more than 50% patients with pediatric CKD and considered to be a modifiable risk factor for cardiovascular (CVD) morbidity and mortality. Dyslipidemia is defined as the presence of at least one of the following: (a) hypertriglyceridemia (>100 mg/dL at 2-9 years of age or >130 mg/dL at 10-17 years of age), (b) low HDL cholesterol (<40 mg/dL) or (c) high non-HDL cholesterol >145 mg/dl according to the guidelines for cardiovascular health and risk reduction in children and adolescents[3,4].

Although there is evidence that dyslipidemia contributes to initiation and progression of CKD[3], the association between dyslipidemia and renal function in paediatric CKD has been assessed by the Chronic Kidney Disease in Children (CKiD) study[5-7]. Hypertriglyceridemia is considered as the hallmark of uremic dyslipidemia and is a consequence of (a) accumulation of triglycerides and triglyceriderich lipoproteins (TRL) in CKD due to increased production and impaired catabolism and (b) increased apolipoprotein C-III levels inducing an increase in triglyceride levels[8,9]. An increased expression of apolipo-

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protein C-III, (inhibitor of lipoprotein lipase (LPL) that breaks down triglycerides), has been reported in vascular endothelial cells of skeletal muscle blood vessels and other cells that utilize fatty acids for their energy consumption[10-12]. One study evaluated the association between dyslipidemia and increased carotid intimamedia thickness[13] and reported a positive association between increased carotid intima-media thickness with elevated levels of total serum cholesterol, triglycerides, and LDL-cholesterol in pediatric CKD patients[13]. The treatment of dyslipidemia in children is still controversial and very few trials have shown reduction in mortality after therapy[14-16]. However, statins have shown significant reduction in cardiovascular morbidity in adult CKD patients, so are the preferred treatments in paediatric cases as well[16,17].

Serum lipid levels vary depending on age, puberty and gender. They are slightly lower in girls than the boys while young adults with CKD have at least 10-fold higher risk of CVD mortality compared to the general population[18-19]. The underlying glomerular renal pathology and duration of proteinuria have also been reported to influence the type of dyslipidemia in pediatric and adult patients with CKD[20-22].

The paucity of data in the literature on dyslipidemia in pediatric CKD led us to conduct this study. Our objective was to determine the frequency and pattern of dyslipidemia in patients with ESRD. The results of this study are expected to enlighten the current status of this issue in our paediatric population.

MATERIAL AND METHODS

This cross sectional, observational study was conducted at Nephrology Department, Children's Hospital & the Institute of Child Health, Lahore, Pakistan from September 2016 to November 2017. The study was conducted after approval of its synopsis from ethical review board of the same institution following tenets laid down in Declaration of Helsinki 2011. Informed written consent was obtained from the parents of the patients. With a confidence interval of 95% and to achieve, a sample size of 138 patients was calculated using WHO sample size calculator considering minimum frequency of dyslipidemia to be 50.0%[2].

Children aged 5-15 years, of either gender and diagnosed with end stage renal disease (chronic kidney disease grade V with eGFR less than 15 ml/min/1.73m^2 by modified Schwartz equation) were enrolled in the study using non-probability purposive sampling. All the participants were receiving renal replacement therapy in the form of hemodialysis and continous ambulatory peritoneal dialysis. Patients having significant family history of dyslipidemia, premature cardiac disease, and those with missing data were excluded from the study.

All the patients were subjected to detailed history and physical examination including demographic data, age, gender, weight, height and etiology of CKD. The laboratory investigations including the lipid panel were performed at the beginning of study. To compare the height, weight of our patients with age matched controls, we used the height, weight for age standard deviation scores (SDS) published by World Health Organization (WHO) in 2007. All patients underwent two measurements of blood pressure using manual mercurial instrument and were labeled hypertensive if either or both systolic and diastolic blood pressures exceeded the 95th percentile as described by the national high blood pressure education program working group on high blood pressure in children and adolescents.

Patients were required to observe overnight fast for a minimum of 12 hours for analysis of various types of serum lipid levels. Levels of total serum cholesterol, serum triglycerides, high density lipoprotein (HDL-C), low density lipoprotein (LDL-C) and very low density lipoprotein (VLDL-C) were measured by Pathology Department of Children's Hospital, Lahore. The levels of serum lipids were classified into various subgroups as presented in table-I.

Data was analyzed using SPSS (IBM Statistics, SPSS Inc, Chicago, Illinois, USA,

version 20.0). Quantitative variables like age, height, weight, blood pressure, lipid profile, were presented in form of mean ± SD. Qualitative variables like gender and etiology of CKD were analyzed and presented as frequency and percentages. The data was stratified for gender. The differences in the numerical variables like lipid levels in hemodialysis versus peritoneal dialysis patients were calculated using student's t-test. A *p*-value≤0.05 was considered statistically significant.

RESULTS

There were 138 patients in the study with mean age 11.24 ± 2.37 (range: 5-15) years. There were 99 (71.7%) male and 39 (28.3%) female patients in the study andthe mean ± SD height and weight of the patients was 130.7 ± 15.8 cm and 24.2 ± 0.8kg respectively. The height, weight adjusted for age matched standard scores were-3.1 (range: -4.6 to -1.8), -1.4 (range: -2.1 to -0.1) and 0.6 (-0.7 to 0.6) respectively (table-II). The overall mean systolic and diastolic blood

Table-I: Classification and operational definitions of various lipid levels.

Variable	Normal (Desirable)	Borderline High	High
Total Cholesterol(mg/dl)	<170	170-199	≥200mmol/L
LDL-Cholesterol (mg/dl)	<110	110-129	≥130mmol/L
VLDL-Cholesterol (mg/dl)	<25	25-30	>30mmol/L
Triglycerides (mg/dl)	<130	130-150	>150mmol/L
	Below Normal	Normal	Desirable
HDL Cholesterol(mg/dl)	<40	40-50	>50mmol/L

Table-II: Demographic profile of the study population (n = 138).

Variables	Frequency (n)	Percentage (%)
Age (years)	11.24 ± 2.37 (Range: 7-15) years	
5-10 years	54	39.1
11-15 years	84	60.9
Gender		
Male	99	71.7
Female	39	28.3
Hemodialysis		
Yes	129	93.5
No	9	6.5
CAPD		
Yes	9	6.5
No	129	93.5
Etiology		
Posterior Urethral Valve	27	19.6
Reflux Nephropathy	21	15.2
Nephrolithiasis	27	19.6
Neurogenic Bladder	9	6.5
Nephronophthesis	12	8.7
Glomerulopathy	15	10.9
Hyperoxaluria	9	6.5
Unknown	18	13.0
Height (cm)	130.1 ± 15.8	
Weight (kg)	24.2 ± 0.8	
Blood Pressure (mmHg)		
Systolic	130.5 ± 17.1	
Diastolic	95.2 ± 21.2	

pressures of the study population were 130.5 ± 17.1 and 90.2 ± 21.2 mmHg respectively. The mean systolic blood pressure was 131.2 ± 18.2 and 128.4 ± 16.5 mmHg I males and females respectively (p=0.41). Similarly, the mean diastolic blood pressure was 91.4 ± 21.9 and 89.8 ± 20.1 mmHg in males and females respectively (p=0.69).

The commonest etiologies of CKD were nephrolithiasis and posterior urethral valves (19.6% each), followed by reflux nephropathy (15.2%) and glomerulopathies (10.9%). A significant number 13.0%) of the patients had unknown causes of CKD. One hundred and twenty nine (93.5%) patients were undergoing hemodialysis whereas only 9 (6.5%) were on continuous ambulatory peritoneal dialysis (CAPD) (table-II).

The mean ± SD values of total serum cholesterol, triglycerides, VLDL-C, LDL-C, and HDL-C were found to be 174.0 ± 54.1, 241.2 ± 142.4, 44.3 ± 22.8, 95.2 ± 49.0 and 35.0 ± 10.8 mg/dl respectively. The frequency of abnormally high levels of total serum cholesterol, triglycerides, VLDL-C and LDL-C was found to be 21.7%, 84.8%, 60.9% and 19.6% respectively. Desirable, normal and abnormally low levels of HDL-C were seen in 10.9%, 13.0% and 76.1% of the cases respectively (table-III). The differences in the lipid levels of patients undergoing hemodialysis versus continuous ambulatory peritoneal dialysis are presented in table-IV.

Table-III: Pattern of various lipid levels in pediatric ESRD patients (n=138).

Lipid Type	Normal		Borderline High		High	
	No.	Percentage (%)	No.	Percentage (%)	No.	Percentage (%)
Total Cholesterol	72	52.2	36	26.1	30	21.7
HDL-C	105	76.1	18	13.0	15	10.9
LDL-C	99	71.7	12	8.7	27	19.6
VLDL-C	3	2.2	51	37.0	84	60.9
Triglycerides	12	8.7	9	6.5	117	84.8

HDL-C: High Density Lipoprotein – cholesterol, LDL-C: Low Density Lipoprotein – cholesterol, VLDL-C: Very Low Density Lipoprotein - cholesterol

Table-IV: Differences in the lipid profile of patients on hemodialysis versuson continuous ambulatory peritoneal dialysis (CAPD).

Lipid Profile	Hemodialysis (n=129)	CAPD (n=9)	p-value*
Total cholesterol (mg/dL)	172 ± 55	210 ± 61	0.049
Triglycerides (mg/dL)	238 ±143	289 ± 137	0.30
HDL-cholesterol (mg/dL)	35.6 ± 11.6	37.6 ± 12.6	0.62
LDL-cholesterol (mg/dL)	95 ± 48	135 ± 53	0.018

*Calculated using student's t-test

DISCUSSION

Dyslipidemia is reported in more than 50% patients with paediatric CKD and its prevalence is associated with various determinants like age, sex, BMI, inflammation, serum albumin and treatment modality[2,22]. We reported a frequency of dyslipidemia in 85% children with ESRD undergoing renal replacement therapy in our tertiary care center: 93.5% patients receiving maintenance hemodialysis and 6.5% undergoing CAPD. Hypertriglyceridemia was the most frequently observed lipid abnormality in 84.8% participants while high serum cholesterol, VLDL-C and LDL-C levels were found in 21.7%, 60.9% and 19.6% respectively.

We studied/analyzed incidence of various etiologies of end stage renal disease in our children and found posterior urethral valves (19.6%) and nephrolithiasis (19.6%) followed by reflux nephropathy (15.2%) and glomerulopathy (10.9%).

Another predictor for an abnormal lipid profile in ESRD is treatment modality. In patients on CAPD, high glucose load from the dialysis

fluid might contribute to dyslipidemia[23]. We observed similar pattern in our study. The lipid levels of patients on peritoneal dialysis were abnormally elevated as compared to those of patients on hemodialysis (table-IV). Kronenberg *et al* reported significantly higher levels of LDL-C and triglycerides and low values of HDL-C in patients on CAPD as compared to those on hemodialysis. Similarly, Siamopoulous *et al* reported more atherogenic lipid levels in patients undergoing CAPD than hemodialysis[24].

Since Asians are more susceptible to early onset cardiovascular disease due to higher levels of triglycerides, the presence of raised triglycerides and simultaneous LDL-C levels impart significance to our results in predicting early atheromatous damage in paediatric patients. On the other hand the effects of dyslipidemia in CKD are hard to determine in adult population due to various confounding co-morbidities that overlap and impair effects of one specific variable on the outcome[25].

Our study has strengths and limitations. This was a cross sectional study. We could not determine the temporal causation of CKD events and associated dyslipidemia over a period of time. A cohort study design would have allowed that to do. We recommend future prospective cohort studies to describe the progression of dyslipidemia and related physical events in paediatric patients. Secondly, the differences in the results of various lipid levels in paediatric CKD patients can be explained on the basis of absence of a normative database of lipid levels in children. So studies in the local healthy paediatric population are advised to develop a *de novo* normative database of normal lipid levels in our normal paediatric population[25]. Lastly, we could not recruit normal healthy individuals for comparison. Case control studies are required to compare the values of various lipid levels in healthy and diseased population.

As our study is the first one in the country and includes a large number of children from a single tertiary care center, we consider it a strength asscarce prior trials have been carried out in pre-dialysis patients of CKD in contrast to our ESRD patients on dialysis treatment.

CONCLUSION

Patients with chronic kidney disease are at increased risk of developing cardiovascular diseases. Dyslipidemia is a major predisposing factor of cardiovascular disease related morbidity in such patients. Hypertriglyceridemia, with higher serum levels of VLDL-C and LDL-C are the most commonly deranged lipids in end stage renal disease paediatric patients. It is recommended to screen all the paediatric chronic kidney disease patients for changes in their lipid profile. If derangements are noted, urgent pharmacological therapies may be initiated to delay atherosclerosis and subsequent cardiovascular events.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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