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ORIGINAL ARTICE

Hyperlipidemia in End-Stage Renal Disease Children

Asmaa Ali, Ahmed Fekry Salem, Sahar AL Sharawy and Al Shaymaa Ali
Paediatrics Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

***Corresponding author:**
- Name: Asmaa Mohamed Mohamed Ali
- Paediatrics Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
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- Email: asmamohamed80@gmail.com

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ABSTRACT

Background: Cardiovascular disease is the leading cause of death in chronic kidney disease children (CKD). Due to their susceptibility to accelerated atherosclerosis, these children are classified as having the greatest level of cardiovascular risk in the American Heart Association's paediatric consensus guidelines for cardiovascular health. Our study intended to improve the early diagnosis of atherosclerosis in children with End-Stage Renal Disease (ESRD). **Methods:** a case-control study involved two groups, ESRD group was 20 cases, males represented 60%, and females represented 40%, the median age was 13 years ranging from 6-18 years, they were on regular haemodialysis, which was done three times per week for four hours with standard bicarbonate dialysis. Haemodialysis was carried through an upper limb arteriovenous fistula by Fresenius medical care 4008 S machine made in Germany. Control: apparently, healthy 25 children of matched age and sex came from outpatient for minor diseases and patient relatives. **Results:** There was a statistically significant reduction in BMI in patients with ESRD compared to control. ESRD patients also had higher systolic and diastolic blood pressure, urea, creatine, CRP, TGS, and PTH than control subjects. **Conclusions:** The most prevalent Dyslipidaemia in ESRD was hypertriglyceridemia, low HDL, increased LDL, and total cholesterol.
Keywords: Chronic Kidney Disease, Atherosclerosis, End-Stage Renal Disease & ESRD.

INTRODUCTION

Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) children [1]. Due to their susceptibility to progressive atherosclerosis, these children are classified as having the greatest level of cardiovascular risk in the American Heart Association's paediatric consensus guidelines for cardiovascular health. Atherosclerosis begins early in life and is related to high blood pressure, dyslipidaemia, obesity, as well as impaired glucose metabolism [2]. Increased oxidative stress in the setting of uraemia in end-stage renal disease (ESRD) accelerates atherosclerosis by promoting enzymatic alteration of circulating lipids and lipoproteins, endothelial dysfunction through disruption of nitric oxide (NO) pathways, and inflammation [3]. Our study attempted to significantly raise the early diagnosis of atherosclerosis in individuals with ESRD.

METHODS

A case-control study was conducted in the nephrology unit, outpatient nephrology clinic, at Zagazig University Paediatric Hospital, Faculty of Medicine, Zagazig University from April 2019 to September 2019. Before conducting the study, approval was acquired from the Institutional Review Board (IRB) and Ethical Committee of Zagazig University's faculty of medicine. Additionally, all participants provided written consent. The study was done according to the code of ethics of the world medical association (Declaration of Helsinki) for studies involving humans.

This study included two main groups; ESRD group was 20 cases, males represented 60%, and females represented 40%, the median age was 13 years ranging from 6-18 years, they were on regular haemodialysis, which was done three times per week for four hours with standard bicarbonate dialysis.

Haemodialysis was carried through an upper limb arteriovenous fistula by Fresenius medical care 4008 S machine made in Germany. The Control group, apparently healthy 25 children of matched age and sex, came from outpatient for minor diseases and patient relatives. Inclusion Criteria were age from 3-18 years, Children with ESRD with GFR less than 15 ml/min/1.713m² for more than three months. Exclusion Criteria were individuals younger than three and also who were older than 18 years old, coexisting primary cardiovascular abnormalities, hyperlipidaemia among family members with a family history of early atherosclerosis/stroke, statin medication as well as acute kidney dysfunction/injury at the period of enrolment.

Full medical history including age, sex, disease onset, course, duration, fatigue, bone pain, uremic symptoms, oedema, period of dialysis setting, frequency/week and filter size was taken. Medications for hypertension including beta-blockers (BB), calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEi), hypercholesterolemia (statin), cardiac and kidney support were documented. General Examination including demographic characteristics (age, gender) and anthropometric measurements (weight, height, and BMI) were determined using the formula {Weight kg/(height m)²}, HT z score WT z score and they were calculated by the following equation[(measured value - average value in reference population)/standard deviation of the reference population] according to (London School of Hygiene and Tropical Medicine, 2009) [4], general appearance, colour, decubitus, body built, skin lesion, blood pressure and pulse were examined. Systemic Examination including the abdomen for ascites and abdominal enlargement, chest for chest pain and crackles, heart for enlarged pericardium and abnormal heart sound was done. Regional Examination: Lower limb and genitalia for LL oedema, genital oedema, arthritis, LL deformity were examined. Head and neck examination for periorbital oedema, throat infection, and discoid lupus were examined.

Laboratory Investigation: CBC: (haemoglobin percentage, white blood cells, and platelet) investigated by an automated cell counter (Sysmex-K-21). CRP investigated by (Cobas 8000), Calcium and phosphorus: investigated by (Cobas 8000), creatinine, urea and albumin: investigated by (Cobas 8000), Lipid profile method: Photometry is used to determine the lipid profile; the instrument is a Roche diagnostics Cobas 8000. As per the American Heart Association's paediatric consensus guidelines, dyslipidaemia is described as the occurrence of at least one of those mentioned below: (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 (total cholesterol – HDL) >145 mg/dl [5] , PTH: immunoassay investigated by chemiluminescence, using Cobas 6000(e601) from Roche diagnostics, Proteinuria: investigated by dipstick. ***Statistical analysis*** SPSS version 23 was used to process the data. It was used to validate, enter, as well as analyse the data. The following statistical methods were employed to analyse the present study's findings. The qualitative variables were expressed as numbers and percentages, whereas the quantitative data were expressed as mean + standard deviation (SD). Categorical results were then compared and quantified using the chi-square test. The significance level was set at P-value <0.05 for chi-square and when the OR's confidence interval did not include 1.

RESULTS

There was no statistically significant difference in demographic data regarding age between patient groups and control, but there are increases in male percentage in ESRD and NS. LN group was female only **(Table 1)**. Also, there was a statistically significant decrease in BMI in ESRD compared to the control group. Weight showed no statistical difference in the studied groups. Weight Z score showed no statistical significance in studied groups **(Table 2)**. Disease duration median is 4 years, and the range is (0-11) years **(Table 3)**. Obstructive uropathy causes were the most common cause of ESRD **(Table 4)**. The most frequent findings in ESRD were pallor, chest pain, dyspnoea, fatigue, and osteodystrophy **(Table 5)**.

The carvedilol, Amlodipine, and captopril were the most frequent cardiac support drugs in ESRD **(Table 6)**. A significant statistical increase in systolic and diastolic blood pressure in the ESRD group compared to the control **(Table 7)**. Besides, there was a statistically significant decrease in HGB in the ESRD group compared to the control, an increase in urea, creatinine, phosphorus, and CRP in ESRD compared to the control **(Table S1)**.

In addition, there was a significant decrease in HDL in ESRD compared to control. There was a significant increase of TGS in ESRD compared to control **(Table S2)**. The increased triglycerides and

decreased HDL level were the most prominent type of dyslipidaemia in ESRD **(Table S3)**. On the other hand, there was a statistically significant increase of PTH in ESRD compared to control **(Table S4)**.

Table 1: Demographic data in end-stage renal disease (ESRD) and control

		ESRD(20)		Control(25)		Chi square test	
		No	%	No	%	x^2	p-value
Sex	Female	8	40.0%	12	48.0%	15.576	0.001
	Male	12	60.0%	13	52.0%		
Age (year)	Median	13		11		9.878*	0.021*
	range	6-18		4-18			

Table 2: Anthropometric measurements ESRD and control group

	ESRD (20)		Control (25)		Kruskal Wallis	
	Median	Range	Median	Range	K	p-value
Weight (kg)	34.5	15-55	37	16-56	5.408	0.144
Height (cm)	143.50	98-163	140.00	99-166	-7.945	0.047
BMI	14.80	13.1-22.02	17.50	14.3-24.8	16.382	0.001
Height z score	0.51	-1.63-1.43	0.35	-1.59-1.57	7.945	0.047
Weight z score	0.07	-2.28-1.47	0.24	-1.19-1.54	5.810	0.121

Table 3: Disease duration in end-stage renal disease (ESRD)

	ESRD (20)	
	Median	Range
Disease Duration (years)	4	0-11

Table 4: Underlying causes of ESRD

Cause	No (20)	%
Obstructive uropathy	7	35%
Congenital causes	4	20%
Unknown cause	3	15%
Nephritis	2	10%
NS FSGS	2	10%
Nephrolithiasis	1	5%
Microangiopathy HUS	1	5%

Table 5: Frequency of clinical findings at ESRD

	ESRD	
	No (20)	%
Ascites	1	5.0%
Bloody stool	0	0.0%
Pallor	10	50.0%
Chest pain	6	30.0%
Dyspnea	6	30%
Fatigue	6	30%

	ESRD	
	No (20)	%
Chest infection	**1**	**5%**
Skin rash	**0**	**0.0%**
Dwarfism,	**1**	**5..0%**
Hypothyroidism	**1**	**5.0%**
Hypertensive Encephalopathy	**1**	**5.0%**
Osteodystrophy	**4**	**20.0%**
Bone pain	**1**	**5.0%**
Arthritis	**0**	**5%**
Lower limb edema	**3**	**15.0%**
Proteinuria by dipstick	**0**	**0.0%**

Table 6: Cardiovascular drugs administered in ESRD

Cardiac Support	ESRD	
	No (20)	%
Amlodipine	**14**	**70%**
Captopril	**14**	**70%**
Prazosin	**3**	**15.0%**
Carvedilol	**14**	**70.0%**
Propranolol	**4**	**20%**
Digitalis	**1**	**5.0%**

Table 7: Blood pressure in ESRD and control groups

		ESRD	Control	one-way ANOVA	
		Mean SD	**Mean SD**	**f**	**p-value**
Blood pressure (mmHg)	systolic	122.00± 16.09	96.80± 10.69	14.069	<0.001
	Diastolic	80.00± 11.24	63.60± 7.57	9.069	<0.001
Post hoc					
		ESRD VS control			
Systolic		**0.001**			
Diastolic		**0.001**			

DISCUSSION

Atherosclerosis is a chronic inflammatory disease that affects the arteries. Atherosclerosis starts with the fatty streak, which causes the accumulation of lipid-rich foam cells in the artery's intimal layer. Atherosclerosis begins with lipid retention, accompanied by chronic inflammation at vulnerable areas in the walls of the main arteries. Pathologic intimal thickening results in fatty streaks, fibrous cap atheroma, and plaques, all of which eventually result in sudden cardiac arrest [6].

Endothelial damage contributes to the development of atherosclerosis. Turbulent blood flow results in endothelial dysfunction; it reduces NO release; vascular disease starts early in the course of CKD and progresses rapidly on dialysis. According to research findings, 20% of children on dialysis acquire vascular calcification throughout the first ten years of their lifetime [7].

We aimed in this study to investigate preclinical atherosclerosis in ESRD in the pediatric population.

This study consisted of 45 children (ESRD), 20 cases on regular hemodialysis, and control 25 healthy children of matched age and sex. Male sex in ESRD was 60%. This agrees with [8] it was 60%. BMI is lower in ESRD compared to control. This could be as a result of comorbidities such as malnutrition, metabolic acidosis, mineral as well as bone diseases, anaemia, fluid, and electrolyte imbalances [9]. This is consistent with the findings of [10], who discovered that growth outcomes in a contemporary cohort of children with CKD remain unsatisfactory. Metabolic acidosis interventions as well as overcoming limitations to recombinant human growth hormone use, could increase growth in this demographic [10].

Height and height Z scores were detected non significantly different in ESRD than control, denoting that ESRD was not affected. This may be due to the age difference between ESRD and control as ESRD are older than the control group. [11]. Found that children with CKD were shorter. Weight and Weight Z score medians show no statistically significant difference due to age difference between subgroups. This comes in agreement with [11], who found no difference in weight between CKD children with GFR of 38.8± 10.8 ml/1.73 m2/min, and control, regarding weight.

We found that the incidence of various etiologies of (ESRD) was obstructive causes (VUR, neurogenic bladder, posterior urethral valve) (35%) and followed by congenital causes (2 PCKD, 2 bilateral atrophy) (20%), unknown causes (15%), nephritis (10%), FSGS (10%), nephrolithiasis (5%) and microangiopathy HUS (5%). In NS, 14 cases were infrequent relapse, 3 cases were frequent relapse, and 3 cases were SRNS.

The most frequent clinical findings in ESRD are pallor, chest pain, dyspnea, fatigue, and osteodystrophy. Carvedilol, Amlodipine, and captopril were the most frequent cardiac support drug used in ESRD, representing 70% and one patient on digoxin. Similarly, drugs used in [12] study in hemodialysis patients were calcium-channel blockers represent (46.6%), ACE inhibitors (60%), β-blockers represent (50%), and two patients on digoxin.

There was a significant statistical increase in systolic and diastolic blood pressure in the ESRD group compared to the control; this agrees with [13], who found that 60% of patients with CKD with GFR less than 60 are on antihypertension medication. [11] found that children with CKD had higher systolic and diastolic blood pressures.

There was a statistically significant decrease in HGB in the patient group compared to the control; there was a statistically significant increase of pH and creatinine in the patient group compared to control and a significant increase of urea in ESRD compared to control. [1] discovered that children undergoing continuous dialysis had significantly higher BUN, serum phosphorus, calcium-phosphorus ion product, as well as parathyroid hormone (PTH) concentrations than children with chronic renal insufficiency (CRI) with a GFR of less than 60 mL/min (20-75).

Our study showed a statistical increase of CRP in ESRD compared to the control group. [12] concluded that CRP values were increased in CKD. The consequences of Dyslipidemia on ESRD are challenging to detect in adults owing to the presence of numerous confounding comorbidities that overlap and impair the impact of a single variable on the outcome [13]. Although HDL is classified as antiatherogenic, it might have detrimental vascular consequences in those with cardiovascular disease, diabetes, or inflammatory diseases. It is uncertain what effect renal insufficiency has on HDL characteristics [14]. LDL-C is thought to be a reliable prognostic marker of endothelial dysfunction. Native LDL cholesterol has been shown to cause endothelial dysfunction by pro-oxidant events [15] or by increasing asymmetric dimethylarginine (ADMA), an endogenous inhibitor of eNOS [16]. Several other mechanisms have been proposed, including decreased eNOS production and suppression of NO production by oxidized LDL cholesterol [17].

There was a significant decrease in HDL in the ESRD group compared to the control. The most prevalent Dyslipidemia in ESRD was hypertriglyceridemia, low HDL followed by increased LDL and total cholesterol levels (60%, 65%, 5%, 5%), respectively. This was consistent with the findings of Chaudhry et al. (2019) [15], who discovered that hypertriglyceridemia was the most often seen lipid disorder in 84.8 % of patients, followed by elevated blood cholesterol and LDL-C values in 21.7 % and 19.6 %, correspondingly.

Renal hyperparathyroidism (rHPT) is a frequent complication of CKD that is defined by high parathyroid hormone levels as a result of calcium, phosphate, as well as vitamin D homeostasis

disturbances. Cardiovascular and bone disorders are more prevalent in patients with rHPT. The Kidney Disease: Improving Global Outcomes guidelines propose that all individuals with CKD stage 3 (estimated glomerular filtration rate, 60 mL/min/1.73 m2) undergo rHPT screening as well as management [16]. In this study, there was a statistically significant increase of PTH in ESRD compared to control. This runs parallel to [17] study, which found a significant increase in PTH in children with GFR less than 60 compared to the control.

CONCLUSIONS

Based on the findings of this study, we can reveal that hypertriglyceridemia, low HDL, as well as elevated LDL and total cholesterol were the most common dyslipidemia in patients with ESRD.

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No funds were received.

DECELERATION OF INTEREST

The authors report no conflicts of interest.

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Supplement: Table S1, Table S2, Table S3, Table S4

Table S1: Laboratory findings in ESRD and control group

	ESRD (20)		Control (25)		one-way ANOVA/	
	Mean SD		Mean SD		f	p-value
HGB(mg/dl)	9.85± 1.73		12.24± 1.39		12.583	**<0.001**
WBCS×10³	6.85± 2.35		7.84± 2.10		0.708	0.550
Albumin (mg/dl)	4.10± 0.45		4.29± 0.46		8.897	**<0.001**
Ca (mg/dl)	8.93± 0.74		9.77± 0.53		9.667	**0.001**
Ph (mg/dl)	6.05± 1.36		4.36± 0.64		12.690	**<0.001**
	Median	**Range**	**Median**	**Range**	**Kruskal Wallis**	
PLT ×10³	240	118-397	265	165-465	7.346	0.062
Urea (mg/dl)	54	25-148	9	1-18	48.159	**0.001**
CRP (mg/dl)	1.85	0.1-15.22	0.30	0.1-0.5	46.533	**0.001**
Creatinine(mg/dl)	8.05	4.59-11.5	0.40	0.30-0.60	**49.83**	**0.001**
Post hoc test						
	ESRD VS control					
HGB (mg/dl)	**0.001**					
Urea (mg/dl)	**0.017**					
Creatinine (mg/dl)	**0.001**					
Albumin (mg/dl)	0.407					
Ca (mg/dl)	0.173					
Ph (mg/dl)	**0.001**					
CRP(mg/dl)	**0.001**					

Table S2: Lipid profile in ESRD and control group

	ESRD (20)		Control (25)		one-way ANOVA	
	Mean SD		**Mean SD**		**f**	**p-value**
Cholesterol(mg/dl)	147.65 26.26		135.60 31.05		10.564	<0.001
HDL (mg/dl)	39.25 11.86		64.88 11.45		38.098	0.004
	Median	**Range**	**Median**	**Range**	**Kruskal Wallis**	
TGS (mg/dl)	132.1	61-218	126.9	42-193.1	9.074	0.028
LDL (mg/dl)	91.6	45.2-131	74.2	30-99.8	43.662	0.001
Post hock test						
	ESRD VS control					
Cholesterol(mg/dl)	0.545					
TGS (mg/dl)	0.001					
HDL (mg/dl)	0.001					
LDL (mg/dl)	0.321					

Table S3: Abnormal lipid profile level according to American heart association guidelines (AHA) in paediatric

	ESRD (20)
Cholesterol(mg/dl)	5%
TGS (mg/dl)	60%
HDL (mg/dl)	65%
LDL (mg/dl)	5%

Table S4: Parathormone hormone (PTH) in ESRD and control group

	ESRD (20)		Control (25)		Kruskal Wallis	
	median	**Range**	**median**	**Range**	**K**	**p-value**
PTH (mg/dl)	243	108-1070	29.8	7-91.5	44.023	0.001
Post hoc test						
	ESRD VS control					
PTH (mg/dl)	0.001					

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