Original Article

Hemodialysis versus Hemodiafiltration: Pulmonary Functions variation in Children with End Stage Renal Disease

Ahmed H. Hassan[1], Magda Y. El Seify[2], Sherif M. Hussein[3], Mahitab M. Hussein[2]

1- Nephrology and Dialysis Unit, Pediatrics Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
2- Pulmonology Unit, Pediatrics Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
3- Ministry of Health and Population, Egypt.

ABSTRACT

Introduction: End-stage renal disease (ESRD) impacts the pulmonary system through hemodynamic instability, endothelial injury, accumulation of toxins, and uremia.

Aim of the study: This study aims to measure pulmonary functions using spirometry and serum endothelin-1 levels among pediatric patients with ESRD before and after dialysis using different hemodialysis modalities.

Methods: This study included fifteen patients on regular conventional hemodialysis and fifteen age and gender-matched patients on regular hemodiafiltration. Serum endothelin-1 levels were measured one hour before and after dialysis sessions. Patients underwent pulmonary function examinations using spirometry to measure the forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) to determine the pattern of pulmonary affection.

Results: There was a significant difference in endothelin-1 levels between both groups before dialysis sessions; however, it became insignificant after dialysis ($p = 0.03$, $p = 0.07$, respectively). Pulmonary function tests (PFT) revealed restrictive lung disease in 73.3% of patients on hemodialysis and 60% of patients on hemodiafiltration. Spirometry readings and the pattern of lung affection were comparable between the two studied groups. Endothelin-1 levels significantly increased post-dialysis in both groups ($p < 0.001$) and were higher in the hemodialysis group pre-dialysis ($p = 0.03$). There was a negative correlation between the duration of dialysis and endothelin-1 levels and PFT parameters in both groups. Endothelin-1 levels were negatively correlated with pre-dialysis PFT parameters ($p < 0.05$).

Conclusion: Pediatric patients with ESRD on either conventional hemodialysis or hemodiafiltration can suffer from silent restrictive lung disease. Routine PFT is recommended for patients on regular dialysis.

KEYWORDS

Pulmonary functions; spirometry; endothelin; end stage renal disease; hemodialysis

Corresponding author: Ahmed Hussein Hassan
Position: Associate Professor of Pediatrics
Affiliation: Pediatric Nephrology department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
Address: 130 Osman Bin Affan Street Heliopolis, Cairo, Egypt
E-mail: ahmedh.hassan@med.asu.edu.eg
ORCHID: 0000-0002-5179-9233
Mobile: (+2)01069412333

INTRODUCTION

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) deteriorate kidney function and necessitate renal replacement techniques. Accumulated toxins, fluid, and electrolytes negatively impact all organ functions. [1,2] The respiratory and renal systems interact to maintain the pH, fluid, and electrolyte homeostasis balance. [3] Therefore, ESRD imposes a substantial burden on the lungs of patients on hemodialysis through multiple aspects, including fluid overload, metabolic acidosis, malnutrition, neutrophil entrapment, and chronic inflammatory status. This could lead to impaired bronchial muscular contractility, disturbed pulmonary function, pulmonary edema, pulmonary hypertension, acute respiratory distress, and sometimes, hemosiderosis. [4-8]

Previous studies observed that CKD patients usually attain a restrictive spirometry pattern due to chronic fluid overload. Reduced glomerular filtration rates (GFR) result in pulmonary edema and respiratory muscle dysfunction due to fluid retention. Even in the early stages of CKD, there is a potential role of endothelial dysfunction in both renal and respiratory systems, with concomitant release of endothelin-1. [9,10] However, there is limited evidence exists regarding the impact of hemodialysis modalities on pulmonary function and endothelin-1 levels. This study aimed to measure the impact of different hemodialysis modalities on pulmonary functions using spirometry and endothelin-1 levels in pediatric patients with ESRD on regular hemodialysis. This could reflect the effectiveness of different dialysis modalities in controlling chronic fluid load before and after dialysis sessions.

METHODS

Study design and settings: This prospective study was conducted in the hemodialysis unit of Ain Shams University Children's Hospital from April 2022 to September 2022.

Study population: The study included thirty children and adolescents, under the age of 18 years, who were diagnosed with ESRD and were on regular hemodialysis. Enrolled patients were consecutively recruited and followed up for at least three months. Patients were equally distributed into two groups: one group on conventional hemodialysis and another group on hemodiafiltration.

Eligibility criteria: All enrolled patients were children diagnosed with ESRD according to the 2019 Kidney Disease Improving Global Outcome (KDIGO) guidelines.[11] Both genders were included with ages ranging between 6 and 18 years. Enrolled patients were on regular dialysis for at least 3 months. Patients with autoimmune diseases, cardiovascular, hepatic, or known pulmonary disorders were excluded from this study.

Sample size: All subjects were selected by a simple randomization technique, using standard sample size calculations by the Epi Info 7 program. A sample size calculation was not conducted in this study due to its exploratory nature. A convenience sample was used, consisting of all patients who met the inclusion criteria and consented to participate within the study timeframe.

Study tools: All participants were subjected to the following, along with laboratory findings, one hour before and after sessions of dialysis. A detailed medical history was collected, including age, gender, duration of the disease,

etiology of ESRD, duration of dialysis, and dialysis-related respiratory symptoms. Through examination was done, including vital signs, anthropometric measures, full general examination, cardiac and abdominal examination, and a detailed chest examination. Laboratory investigations included complete blood count (CBC) using Coulter counter (T660), C-reactive protein (CRP), serum creatinine and urea, and K level. Serum endothelin-1 level was measured using an advanced AVL 995 analyzer.

Pulmonary function tests (PFT) were done using spirometry (JAEGER, apparatus, CareFusion Germany 2011) according to ERS/ATS criteria.[12] The following parameters were examined: Forced expiratory volume in the first second (FEV1), expressed as % of the predicted value. Forced vital capacity (FVC) was expressed as % of the predicted value. FEV1/FVC ratio was measured, being the ratio between forced expiratory volume in one second and forced vital capacity. Maximal mid-expiratory flow between 25-75% of expired capacity (MMEF 25-75%) was expressed as % of the predicted value.

Interpretation of the results: Normal FEV1 >80%, normal FVC >80%, and normal FEV1/FVC ratio >80% were considered normal lung functions. Decreased FEV1 <80%, decreased FEV1/FVC ratio <80%, and normal FVC >80% were considered obstructive lung functions. Decreased FVC <80%, normal or increased FEV1/FVC >80%, and normal or decreased FEV1 <80% were considered restrictive lung function. Decreased FVC <80%, decreased FEV1/FVC ratio <80%, and decreased FEV1 <80% were considered mixed lung function.

STATISTICAL ANALYSIS

Statistical Package for Social Science (SPSS; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows was used for all statistical analyses. Data was collected, tabulated, and analyzed using the appropriate statistical methods. Comparison between two independent groups for nonparametric data using Mann-Whitney U Test. Wilcoxon signed rank test for comparison between two dependent groups was used for non-parametric data. Ranked Spearman correlation test was used to study the possible association between each two variables within each group for non-parametric data. Chi-square test ($\chi 2$) to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. Z-test was used when appropriate. McNemar test was used when appropriate. A P-value of < 0.05 was considered significant.

RESULTS

Thirty patients were recruited in the study, with a median age (IQR) of 14 (10-15) years, including 14 males and 16 females, equally distributed in the 2 subgroups. The median (IQR) duration of hemodialysis in the first group was 4.5 (3-8) years, and in the second group, the median (IQR) duration of hemodiafiltration was 3 (2-6) years, with a non-significant difference ($p = 0.3$). The body mass index of both groups was comparable ($p = 0.5$); however, the median body weight and height were higher in the patients on hemodiafiltration ($p = 0.01$, $p = 0.002$, respectively) **Table 1**. All the participants had controlled blood pressure

and normal respiratory and heart rates.

Basic laboratory investigations, including CBC, CRP, K level, serum creatinine, and serum urea, did not show significant differences between the 2 studied groups. There was a significant elevation of endothelin-1 levels after dialysis in both groups ($p < 0.001$) **Table 2**. When comparing both groups, there was a significant difference in endothelin-1 levels before dialysis sessions ($p = 0.03$); however, levels were comparable after dialysis sessions ($p = 0.07$).

PFT assessment using spirometry did not differ among the studied groups in all the parameters after dialysis, with all p-values > 0.05 **Tables 3 and 4**.

Spirometry readings and the pattern of lung affection showed a non-significant difference between the two studied groups. However, the dialysis duration was negatively correlated to endothelin-1 levels and PFT parameters in both groups, which was statistically significant, with all p-values < 0.05 **Table 5**. Endothelin-1 level was negatively correlated to the pre-dialysis PFT parameters **Table 6**.

Table 1: Anthropometric measurements of all the studied patients

Variables / Median (IQR)	Group 1 Hemodialysis (n=15)	Group 2 Hemodiafiltration (n=15)	T*	P
Weight (kg)	23.5 (20.5– 30.0)	30.5 (27.0 – 34.5)	2.6	**0.01***
Height (cm)	118.0 (108.0 – 132.0)	137.0 (131.0 – 141.0)	3.1	**0.002***
BMI (kg/m^2)	16.8 (15.0 – 18.9)	16.0 (15.4 – 17.2)	0.7	0.5

BMI: body mass index, IQR: interquartile range, *Mann-Whitney U Test, A p-value < 0.05 is considered statistically significant

Table 2: Serum endothelin-1 levels before and after dialysis in the 2 studied groups

Endothelin-1 (ng/dl)	Before dialysis Median (IQR)	After dialysis Median (IQR)	T*	P
Group 1 (hemodialysis)	35.0 (10.0 – 55.0)	100.0 (70.0 – 135.0)	3.1	**0.001****
Group (hemodiafiltration)	25.0 (15.0 – 35.0)	85.0 (75.0 – 150.0)	3.2	**0.001****

**A p-value < 0.05 is considered statistically significant

Table 3: Spirometry reading interpretation of the patients on hemodialysis

Spirometry parameters**	Pre-dialysis (n=15) Median (IQR)	Post-dialysis (n=15) Median (IQR)	T*	P
FEV1 % predicted	76.9 (66.7 – 89.0)	79.3 (73.7 – 94.3)	1.1	0.3
FVC % predicted	68.0 (59.5 – 83.2)	71.4 (65.1 – 86.5)	0.9	0.3
FEV1/FVC ratio	97.5 (90.8 – 98.7)	97.9 (89.7-92.9)	0.3	0.7
MMEF 25-75% predicted	68.0 (55.2 – 106.0)	79.6 (54.7 – 107.4)	0.6	0.5
Pulmonary Functions*	**Pre-dialysis n (%)**	**Post-dialysis n (%)**		
Normal	4 (26.7)	5 (33.3)	--	--
Restrictive	11 (73.3)	9 (60.0)	--	--
Obstructive	0 (0.0)	0 (0.0)	--	--
Mixed	0 (0.0)	1 (6.7)	--	--

*McNemar test p>0.05, **Wilcoxon signed rank test (WS), A p-value < 0.05 is considered statistically significant
Normal FEV1 >80%, normal FVC >80%, and normal FEV1/FVC ratio >80% were considered normal lung functions. Decreased FEV1 <80%, decreased FEV1/FVC ratio <80%, and normal FVC >80% were considered obstructive lung functions. Decreased FVC <80%, normal or increased FEV1/FVC >80%, and normal or decreased FEV1 <80% were considered restrictive lung function. Decreased FVC <80%, decreased FEV1/FVC ratio <80%, and decreased FEV1 <80% were considered mixed lung function.

Table 4: Spirometry reading interpretation of the patients on hemodiafiltration

Spirometry parameters**	Pre-dialysis (n=15) Median (IQR)	Post-dialysis (n=15) Median (IQR)	T*	P
FEV1 % predicted	73.8 (62.9 – 87.2)	82.5 (66.5 – 94.4)	1.2	0.2
FVC % predicted	67.9 (62.6 – 83.0)	77.4 (69.1 – 83.9)	0.6	0.5
FEV1/FVC ratio	94.7 (87.5 – 97.3)	96.5 (87.9 – 98.8)	1.0	0.3
MMEF 25-75% predicted	72.2 (49.5 – 90.3)	91.8 (47.2 – 111.7)	1.5	0.1
Pulmonary Functions*	**Pre-dialysis n (%)**	**Post-dialysis n (%)**		
Normal	4 (26.7)	4 (26.7)	--	--
Restrictive	9 (60)	10 (66.7)	--	--
Obstructive	1 (6.7)	1 (6.7)	--	--
Mixed	1 (6.7)	0 (0.0)	--	--

*Mc Nemar test p>0.05, **Wilcoxon signed rank test (WS), A p-value < 0.05 is considered statistically significant
Normal FEV1 >80%, normal FVC >80%, and normal FEV1/FVC ratio >80% were considered normal lung functions. Decreased FEV1 <80%, decreased FEV1/FVC ratio <80%, and normal FVC >80% were considered obstructive lung functions. Decreased FVC <80%, normal or increased FEV1/FVC >80%, and normal or decreased FEV1 <80% were considered restrictive lung function. Decreased FVC <80%, decreased FEV1/FVC ratio <80%, and decreased FEV1 <80% were considered mixed lung function.

Table 5: Correlation between the dialysis duration and endothelin-1 level and PFT

Spirometry parameters	Duration of hemodialysis (n=15)		Duration of hemodiafiltration (n=15)	
	r*	P	r*	P
FEV1% predicted:				
Before dialysis	-0.5	0.04*	- 0.6	0.009*
After dialysis	-0.7	0.001*	- 0.7	0.005*
FVC% predicted:				
Before dialysis	- 0.6	0.03*	- 0.7	0.002*
After dialysis	-0.6	0.01*	- 0.6	0.01*
FEV1/FVC ratio:				
Before dialysis	- 0.5	0.03*	- 0.6	0.01*
After dialysis	-0.5	0.04*	- 0.7	0.003*
$MMEF_{25-5\%}$ predicted:				
Before dialysis	-0.6	0.01*	-0.7	0.005*
After dialysis	-0.5	0.04*	-0.6	0.02*
Endothelin-1				
Before dialysis	0.7	0.04*	0.6	0.02*
After dialysis	0.6	0.02*	0.6	0.01*

*Ranked Spearman Correlation Test, A p-value < 0.05 is considered statistically significant

Table 6: Correlation between endothelin-1 level and PFT in the two studied groups

Spirometry parameters	Endothelin-1 level in group 1 (n=15)		Endothelin-1 level in group 2 (n=15)	
	r*	P	r*	P
FEV1% predicted:				
Before dialysis	-0.4	0.01	-0.4	0.02
After dialysis	-0.2	0.4	-0.3	0.1
FVC% predicted:				
Before dialysis	0.4	0.01	0.3	0.04
After dialysis	-0.1	0.6	-0.3	0.1
FEV1/FVC ratio:				
Before dialysis	-0.5	0.01	-0.4	0.03
After dialysis	0.1	0.7	0.04	0.8
$MMEF_{25-5\%}$ predicted:				
Before dialysis	-0.4	0.02	-0.5	0.01
After dialysis	-0.3	0.3	-0.4	0.01

*Ranked Spearman Correlation Test, A p-value < 0.05 is considered statistically significant

DISCUSSION

This study assessed the impact of different hemodialysis modalities on pulmonary functions using spirometry and endothelin-1 levels in children with ESRD. Restrictive lung patterns were identified by PFT post dialysis in 60% of patients in each group. Taking into consideration that all patients were on regular dialysis for at least 3 months, the noticed fluctuation in PFT before and after sessions of hemodialysis and the stable pattern of PFT among patients on hemodiafiltration illustrates that the latter modality of dialysis could achieve better pulmonary control, without fluctuating alveolar edema or change in the PFT parameters. In parallel to these findings, patients on hemodiafiltration had significantly better weight and height than patients on hemodialysis; however, BMI was comparable between both groups. This can be attributed to the achieved stable pattern of the pulmonary parameters among those patients, leading to improved growth. However, both modalities of dialysis were associated with a relatively high frequency of restrictive lung disease post-dialysis, which can be explained by ESRD and its etiology.

Restrictive patterns of lung disease were found among 73.3% of the patients on hemodialysis and among 60% of patients on hemodiafiltration before their dialysis session. Persistent restrictive lung disease after dialysis was present among 60% of the patients on hemodialysis, however, patients on hemodiafiltration showed no change, except for one patient who had a mixed type of lung affection before dialysis and a restricted pattern post-dialysis. This favors the fact that patients with restrictive patterns were not affected by hemodiafiltration and is independent of dialysis modality. As the spirometry parameters were negatively correlated to the duration of dialysis in both groups, we cannot guarantee that hemodiafiltration has a better outcome as regards the pulmonary affection, despite the lower number of affected persons. Nevertheless, patients on hemodiafiltration had significantly better growth parameters, which can justify the lower number of patients with pulmonary affection. However, the persistence of the impaired pulmonary functions illustrates the presence of true lung affection in spite of the absence of clinical manifestations.

Multiple studies reported the prevalence of restricted lung disease among patients on regular hemodialysis.[1,6,8,13-15] Cury et al. attributed the restrictive lung disease to the chronic and often subclinical pulmonary edema, fluid retention, hypoalbuminemia, interstitial fibrosis and calcification of the lung parenchyma and bronchial tree, and recurrent infections.[14] However, in the current study, radiological examination of the pulmonary tree was not studied in conjunction with PFT. Control of fluid overload in pediatric patients with ESRD on dialysis is the key challenge to control the comorbidities.[16] The value of hemodialysis in improving PFT in adult patients was reported by Momeni et al., in agreement with our results.[4] However, their studied patients were not compared to another group on hemodiafiltration.

As regards endothelin-1 levels, they showed a significant increase after the dialysis sessions in both groups, being more elevated among patients on hemodialysis. Rise of serum endothelin-1 levels in children with ESRD can be attributed to their reduced clearance,

excessive release due to endothelial injury and hemodynamic changes, in addition to impaired metabolism due to uremia, a common finding in multiple studies. [17-19] Hemodialysis is more injurious to the microvasculature than hemodiafiltration, which can justify the paramount elevation in endothelin-1 levels after sessions of hemodialysis. However, in agreement with our findings, Kovačević et al. reported a negative correlation between endothelin-1 levels and PFT parameters, denoting the uremic impact on the lung.[20] Therefore, the higher secretion of endothelin-1 can be augmented by the pulmonary endothelial injury.

LIMITATIONS OF STUDY

The relatively low number of studied patients, lack of sample size calculation, and the lack of a similar adult-aged group to be compared with were the main limitations of this study. Another limitation was that the potential confounding variables, such as nutritional status, physical activity level, underlying etiology of ESRD, presence of anemia, and residual renal function, were not accounted for and could influence pulmonary function outcomes. In addition, the diffusing capacity of the lung for carbon monoxide was not available for assessment, being a parameter for pulmonary function assessment.

RECOMMENDATIONS

Further studies with a larger sample size to ascertain the role of endothelin-1 in the pathogenesis of lung disease in chronic renal failure and the role of ET- ET-antagonists in treatment or prophylaxis, and prevention of chronic renal disease. We recommend further studies to assess the impact of dialysis on diffusing capacity in patients with ERSD, as most patients had a restrictive pattern of PFT.

CONCLUSION

Pediatric patients with ESRD on either hemodialysis or hemodiafiltration may suffer from silent restrictive lung disease. Routine PFT is recommended for patients on regular dialysis. Endothelin-1 level in association with PFT can manifest as a better predictor, however, this needs to be emphasized in further studies.

ABBREVIATIONS

CBC	Complete blood count
CKD	Chronic kidney disease
CRP	C-reactive protein
ESRD	End Stage Renal Disease
FEV1	Forced Expiratory Volume in the First Second
FVC	Forced Vital Capacity
GFR	Glomerular Filtration Rate
IQR	Interquartile Range
KIDGO	Kidney Disease Improving Global Outcome
MMEF	Maximal-Mid Expiratory Flow
PFT	Pulmonary Function Test

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.
All authors have contributed to authorship, have read and approved the manuscript.
Conception and design of study: A Hussien, M Hussein, M El-seify
Acquisition of data: S Moawaad
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Authors declare that they have no conflict of interests
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Ethical approval was obtained from the University Research Ethics Committee in our country, which follows the research ethics of Helsinki. The approval number is FMASU MSO (35/2022).
Consent for publication
Verbal consent was obtained from all the participants after explaining the aim and the method of the research by assuring their right to withdraw from the research whenever they want without any consequences.
Data are available upon request
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