Prevalence of Pulmonary Hypertension in End-stage Renal Disease Patients Undergoing Hemodialysis and Peritoneal Dialysis at a Referral Center in Mashhad, Iran, From 2015 to 2016

Maryam Miri,[1] Sepideh Hejazi,[2] Forough Maghsoudlou,[3] Mahnaz Ahmadi[4]

[1]Kidney transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Mashhad University of Medical Sciences, Mashhad, Iran
[4]Departmentof Cardiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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Introduction. Pulmonary artery hypertension is a serious comorbidityof dialysis in patients with end-stage renal disease. The prevalence of dialysis-induced pulmonary artery hypertension is still a subject of debate. The aim of this study was to determine the prevalence of pulmonary artery hypertension in patients undergoing hemodialysis and peritoneal dialysis.

Materials and Methods. This cross-sectional study was conducted on patients undergoing either hemodialysis or peritoneal dialysis in Montaserieh Dialysis Center in Mashhad, Iran during 2015 and 2016. Pulmonary artery pressure, ejection fraction, and serum levels of calcium, phosphorus, creatinine, and parathyroid hormone were measured.

Results. A total of 50 patients (25 on hemodialysis and 25 on peritoneal dialysis) participated in the study. The mean age of the participants was 34 ± 12 years. The mean pulmonary artery pressure was significantly higher in the hemodialysis group compared to the peritoneal dialysis group ($P < .001$). Serum calcium was significantly higher in the peritoneal dialysis group compared ($P = .04$). Pulmonary artery hypertension was observed in 11 patients (22%), all of whom were in the hemodialysis group. There was a significant negative relationship between serum calcium and pulmonary artery pressure ($P < .01$). Hemodialysis was significantly related to higher pulmonary artery pressure ($P < .001$).

Conclusions. This study revealed a high prevalence of pulmonary artery hypertension among end-stage renal disease patients undergoing dialysis. This study also found a novel significant negative relationship between serum calcium level and pulmonary artery pressure, and hemodialysis was found to be significantly related to higher pulmonary artery pressure.

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INTRODUCTION

Cardiovascular complications are the most common causes of mortality in end-stage renal disease (ESRD) patients.[1,2] Pulmonary artery hypertension (PAH) is among the life threatening cardiovascular complications of ESRD.[3] The gold standard for diagnosis of PAH is right-heart catheterization.[4-6] Due to the cost and difficulty

in performing right-heart catheterization, echocardiography has been described as a reliable alternative in the diagnosis of PAH with an 83% sensitivity and a 72% specificity.[4-6] Pulmonary artery hypertension is defined as systolic pulmonary artery pressure (PAP) greater than 25 mm Hg in resting condition measured by echocardiography.[7,8] Since echocardiography is routinely used to assess the PAP, and due to the fact that echocardiography measures the estimated PAP instead of mean PAP, the cutoff for PAH detection is defined as estimated PAP greater than 35 mm Hg.[9] Pulmonary artery hypertension is a progressive condition, which may induce right ventricular dysfunction and consequently dysfunction in other body organs and result in increased mortality and morbidity and is mostly seen in ESRD patients either before initiation of dialysis or during renal replacement therapy.[1,2]

The prevalence of PAH in ESRD was reported to range from 25% to 60% in previous studies based on echocardiographic assessments, but the prevalence of PAH in ESRD patients undergoing dialysis is not well defined.[8,10-13] The prevalence of PAH has been reported, in a few studies, to vary form 18.8% to 68.8% in hemodialysis and zero to 42% in peritoneal dialysis (PD) patients which was higher than the general population.[14,15] Unfortunately, few published data exist regarding the prevalence of PAH in hemodialysis and PD patients in the Middle East. Regarding the high prevalence of PAH in dialysis patients, it is necessary to identify and manage this life-threatening condition in hemodialysis and PD patients. The aim of this study was to determine the prevalence of PAH in ESRD patients undergoing dialysis.

MATERIALS AND METHODS

Study Population

This cross-sectional study was conducted on ESRD patients undergoing hemodialysis or PD in Montaserieh Dialysis Center, Mashhad, Iran during 2015 and 2016. All patients older than 18 years who were willing to participate in the study were included in the study. Patients were excluded if they had any condition that could affect PAP including cardiomyopathy, obstructive sleep apnea, any obstructive pulmonary disease, thrombotic pulmonary disease, cirrhosis, and portal hypertension as well as any rheumatologic disease that affect PAP including lupus erythematosus and scleroderma. The process and objectives of the study were described to each patient and a written informed consent was obtained from patients who were willing to participate in the study. The study protocol was approved by Mashhad University of Medical Sciences Ethics Committee (registration No, IR.mums. REC.1396.107).

Sample size for this study was calculated based on the previously reported prevalence of PAH among hemodialysis and PD patients considering the prevalence of PAH in hemodialysis and PD patients (0.58% and 0.18% respectively).[16] The calculated sample size for this study was 22 patients in each group. Considering 20% drop out, the final sample size was rounded to 50 patients.

Instruments

All of the 50 patients underwent echocardiography by a cardiologist in order to record systolic PAP and ejection fraction. A PAP value equal to or higher than 35 mm Hg was considered PAH. Laboratory measurements included serum calcium, phosphorus, hemoglobin, creatinine, and parathyroid hormone. Demographic data including age, sex, and underlying cause of ESRD were obtained from the medical records.

Statistical Analysis

The SPSS software (Statistical Package for the Social Sciences, version 21.0, IBM Corp, New York, NY, USA) was used to analyze the data. Continuous data were checked for normality using the Shapiro-Wilk test. Mean and standard deviation were used to describe normally distributed continuous variables while median and interquartile range were used for non-normally distributed variables. Categorical variables were presented using frequency and percentage. The independent sample *t* test was used to compare normally distributed continuous variables between dialysis groups while the non-normally distributed variables were compared using the Mann-Whitney test. The chi-square and the Fisher exact test were used to compare distribution pattern of categorical variables between study groups. Linear regression was used to assess the relationship between PAP and study parameters. The binary logistic regression was used to assess the relation between type of dialysis and study parameters considering PD as reference. The odds

ratio (OR) and 95% confidence interval (CI) for OR were presented for each parameter in binary logistic regression. Values of *P* less than .05 were considered significant.

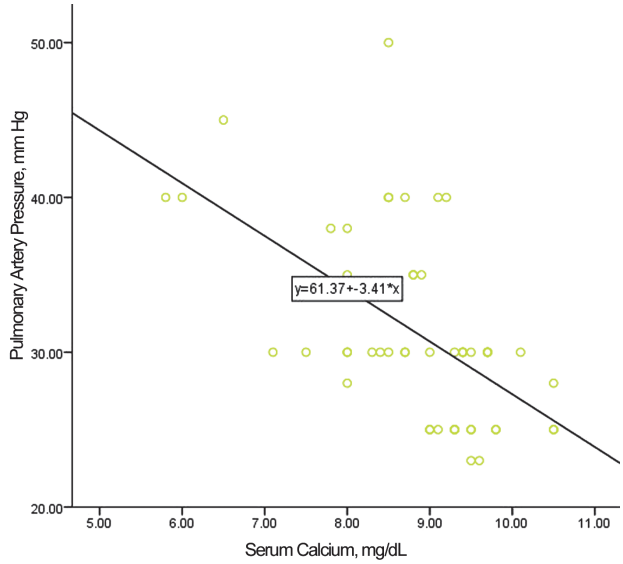
RESULTS

A total of 50 patients (25 hemodialysis and 25 PD patients) participated in the study. The mean age of the patients was 33.88 ± 11.53 years. Twenty-nine patients (58.8%) were male and 21 (41.2%) were female. Comparison of laboratory and echocardiographic characteristics between the two dialysis groups are presented in Table 1.

The most common underlying cause of ESRD was idiopathic (46%), followed by Alport syndrome (6%), diabetes mellitus (10%), nephrotic syndrome (10%), hypertension (8%), focal segmental glomerulonephritis (4%), preeclampsia (4%), Fancony syndrome (4%), mesangioprolipherative glomerulonephritis (4%), congenital anomalies (2%), and reflux nephropathy (2%).

The hemodialysis group had significantly higher PAP ($P < 0.001$) and lower serum calcium ($P = .04$) compared to the PD group (Table 1). Pulmonary artery hypertension was detected in 11 patients (22%) who were all in the hemodialysis group. Linear regression revealed a significant negative relationship between PAP and serum calcium (r = -0.48, $P < .001$; Figure) and a positive relationship between hemodialysis group and higher PAP (r = 0.34, $P = .01$; Table 2).

Binary logistic regression revealed a significant relationship between PAP and hemodialysis group (OR, 1.27; 95% CI, 1.05 to 1.53; $P = .01$; Table 3).



Relationship between pulmonary artery pressure (PAP) and serum calcium level among the studied dialysis patients

Table 2. Relationship Between Pulmonary Artery Pressure and Studied Parameters

Parameter	r (95% Confident Interval)	*P*
Age	0.10 (-0.08 to 0.19)	.42
Female sex	0.22 (-0.34 to 5.85)	.08
Hemodialysis modality	0.34 (1.18 to 7.27)	.01
Hemoglobin	0.08 (-0.46 to 0.90)	.52
Serum creatinine	-0.14 (-0.72 to 0.20)	.26
Parathyroid hormone	-0.09 (0.00 to 0.00)	.45
Serum calcium	-0.48 (-4.33 to -1.38)	< .001
Serum phosphorus	-0.14 (-1.06 to 0.27)	.24
Ejection fraction	-0.20 (-0.24 to 0.02)	.10

DISCUSSION

This study found that the prevalence of PAH was 22% in ESRD patients. This finding was in line with the findings of the previous studies.[8,10-15] The current study finding was interesting because all PAH subjects were in hemodialysis group. This finding might be due to the difference in underlying medical condition between hemodialysis and PD patients. Previous studies have also reported higher prevalence of PAH in hemodialysis patients

Table 1. Characteristics of Studied Patients*

Variable	All n = 50	Hemodialysis Patients n = 25	Peritoneal Dialysis Patients n = 25	*P*
Age, y	33.88 ± 11.53	36.96 ± 11.19	30.80 ± 11.26	.06
Pulmonary artery pressure, mm Hg	31.26 ± 6.19	34.28 ± 6.78	28.24 ± 3.65	< .001
Hemoglobin, g/dL	10.64 ± 2.21	11.04 ± 2.36	10.24 ± 2.02	.21
Serum creatinine, mg/dL	8.32 ± 3.36	8.90 ± 2.53	7.75 ± 3.99	.23
Parathyroid hormone, pg/mL	230.00 (517.58)	245 (502.50)	215 (532.25)	.68
Serum calcium, mg/dL	8.83 ± 1.03	8.54 ± 1.16	9.13 ± 0.79	.04
Serum phosphorus, mg/dL	6.40 ± 2.33	6.42 ± 2.71	6.38 ± 1.45	.95
Ejection fraction, %	54.62 ± 11.27	53.16 ± 11.60	56.08 ± 10.98	.36

*Values are mean standard deviation, except for parathyroid hormone, which is median (interquartile range).

Table 3. Relationship Between Hemodialysis Modality and Studied Parameters

Parameter	Odds Ratio (95% Confident Interval)	*P*
Age	1.03 (0.95 to 1.11)	.46
Female sex	2.86 (0.57 to 14.22)	.20
Hemoglobin	1.13 (0.79 to 1.62)	.50
Serum creatinine	1.17 (0.92 to 1.49)	.20
Parathyroid hormone	1.00 (0.99 to 1.00)	.44
Serum calcium	0.97 (0.38 to 2.48)	.95
Serum phosphorus	0.96 (0.65 to 1.40)	.82
Ejection fraction	1.02 (0.95 to 1.09)	.58
Pulmonary artery pressure	1.27 (1.05 to 1.53)	.01

compared to PD patients.[14,15] Controversial findings were reported in previous studies regarding the prevalence of PAH in PD patients. While a study on 5 PD patients found no cases of PAH, in a study in 2009 on 135 PD patients the prevalence of PAH was reported to be 12.6%.[17] In another study on 36 PD patients the prevalence of PAH was 42%.[8] The reason for the difference in the observed prevalence of PAH in these studies might be due to the difference in the sample size of the studies. It is recommended for further researchers to include larger number of PD and hemodialysis patients in their studies in order to reach a better understanding of the condition in ESRD population undergoing dialysis. Due to the small number of dialysis patients in health centers larger regional or national studies are recommended in order to determine the prevalence of PAH. The other reason for the observed differences between these studies might be due to the use of echocardiography for diagnosis of PAH, which is not the gold standard for diagnosis of PAH and is associated with personal errors.

This study revealed a significant negative association between serum calcium and PAP. The findings of the previous studies regarding the relationship between serum calcium and PAP were inconsistent. While some studies failed to identify a relation between serum calcium and PAH,[13,18] in a study on neonates with PAH, a significant negative association was observed between PAP and serum calcium level.[19] It was previously shown that calcium results in increased vasoconstriction in pulmonary arteries.[20] The exact mechanism of action of calcium in the induction or aggravation of PAH is not yet known. It is suggested that calcium may result in pulmonary artery stiffness by induction of calcification.[4,21,22] In contrast lower serum calcium might also result in increased PAP through its role in the production of parathyroid hormone.[14] Although the observed relation between serum calcium and PAP in the current study did not reveal causative effect, this finding provides evidence for the existence of a relation between serum calcium level and PAH. It is recommended for further researchers to assess the underlying metabolic relations between serum calcium and pulmonary vascular function in dialysis patients. This study also found a significantly higher serum calcium concentration in hemodialysis subjects compared to PD subjects which can indicate a different metabolic condition in ESRD patients undergoing PD compared to hemodialysis. It is recommended for further researchers to assess the relation between serum calcium-phosphate metabolism among hemodialysis and PD patients.

One of the limitations of this study was the small sample size, which was due to time and financial restrictions. On the other hand, one of the strengths of the study was the inclusion of both hemodialysis and PD patients and comparing the study parameters between hemodialysis and PD patients.

CONCLUSIONS

The prevalence of PAH was high among the ESRD patients undergoing dialysis and the risk of developing PAH was higher among the patients who were undergoing hemodialysis. Serum calcium was also detected as a predictor for PAP. Further research is required to identify the reasons behind this finding.

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CONFLICT OF INTEREST

None declared.

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Correspondence to:
Mahnaz Ahmadi, MD
Department of Cardiology, Faculty of Medicine, Mashhad University of Medical Sciences,
9137913316, Mashhad, Iran
Tel: +98 513 854 3031
Fax: +98 513 859 1057
E-mail: ahmadikm@mums.ac.ir

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