Patterns of Pulmonary Hypertension in Patients with Chronic Kidney Disease

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ABSTRACT

Background: Pulmonary hypertension (PH) is often associated with high morbidity and mortality and is recently recognized as a common complication secondary to chronic kidney disease (CKD). Epidemiological data for this disorder across the spectrum of CKD is poorly understood.

Objective: The aim of the work was to detect patterns of PH in patients with chronic kidney disease (CKD).

Patients and methods: This study was carried on 80 patients with CKD who were followed up at outpatient clinics, Aswan University Hospital, Aswan, Egypt. This study was conducted between February 2019 and January 2020.

Results: There was highly statistically significant increase in PH (65 %) in dialytic group and (42.5%) in non-dialytic group, with mean pulmonary artery systolic pressure (PASP) 41.22 ± 11.32 18 to 25 mm Hg in dialytic group versus 33.37± 9.43 mm Hg in non-dialytic group. Also, positive relationship between PH and increase in duration of CKD, but there is no significant relationship with duration of dialysis treatment, hemoglobin level, calcium and phosphorus. Despite a positive correlation between arteriovenous fistula (AVF) flow and PASP, multivariate analysis did not show a significant relation between them.

Conclusion: It could be concluded that pulmonary hypertension is a common finding in CKD patients; the prevalence was highest among patients with end stage renal disease (ESRD) on regular haemodialysis (HD) than those on conservative management. Early detection of PH is important in order to avoid the serious consequences of the disease.

Keywords: Pulmonary Hypertension, Chronic Kidney Disease

INTRODUCTION

Chronic kidney disease is a common condition, and its prevalence is increasing. It is a functional or structural kidney abnormality, lasting for at least three months which could be classified according to etiology, glomerular filtration rate (GFR) and/or albuminuria. Staging of CKD was defined by accepted eGFR thresholds, CKD stage with GFR 90, and CKD stage I with GFR 60–89mL/min/1.73 m2, with evidence of renal damage, CKD stage III with GFR 30–59, stage IV with GFR 15–29, and stage V with GFR<15 mL/min/1.73m^2 [(1)].

Pulmonary hypertension is relatively common in patients with CKD and ESRD. There are many mechanisms can describe the influence of CKD on the pulmonary arteries as left ventricular disorders, volume overload, hyperdynamic circulation due to severe anemia, AVF, sleep disorders, thromboembolism, and others [(2, 3)].

Pulmonary hypertension is a pathophysiological disorder complicating heart, lung, or systemic diseases, with increased morbidity and mortality regardless of its etiology. It is a syndrome characterized by presence of mean pulmonary artery pressure > 25 mm Hg at rest [(3)].

The World Health Organization categorizes PH into 5 distinctive groups based on cause: pulmonary arterial hypertension, PH due to left sided cardiac disease, PH due to lung disease or hypoxia, chronic thromboembolic PH, and PH due to unclear multifactorial mechanisms, respectively [(4)].

There are two methods to measure PH, first of them is right heart catheterization which considered the diagnostic gold standard, and second one is noninvasive transthoracic doppler echocardiography (TTDE) which is used to calculate estimated PASP [(5)].

Using TTDE, measurement of PASP is based on the tricuspid regurgitation jet, a phenomenon that can be recorded in most physiologic and pathologic conditions. In the absence of pulmonary stenosis, PASP is estimated by the calculation of right ventricular systolic pressure by a modified Bernoulli equation and is computed as 4 times the square of maximum tricuspid regurgitation jet velocity (TRV), plus right atrial pressure [(6)].

The aim of this study was to detect patterns of PH in patients with chronic kidney disease.

PATIENTS AND METHODS

This cross-sectional study included a total of 80 CKD patients who were followed up at outpatient clinics, Aswan university hospital, Aswan, Egypt. This study was conducted between February 2019 and January 2020.

Inclusion criteria: Patients from both sex, patients above 18 years old and known CKD patients fulfilled by laboratory and radiological assessment.

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Exclusion criteria: Smokers, cardiovascular diseases which lead to PH, pulmonary diseases such as chronic obstructive lung disease, interstitial lung disease, previous pulmonary embolism, collagen vascular disease and acute renal failure.

Ethical considerations:

This study was approved by the ethical committee of the faculty of medicine in Aswan University. Each patient was private file with non-disclosure policy at data presentation where all presented data do not contain any personal information specifying the identity of any of the patients.

Written informed consent of all the subjects was obtained after verbal and written description about the study. The participants have the right to withdraw from the study at any time without giving any reasons.

The included subjects were divided into two equal groups; **Group I** consisted of 40 patients (20 males, and 20 females with a mean age 46.08± 3.84 years) on conservative management, **Group II** consisted of 40 patients (25males, and 15 females with a mean age 47.51± 12.87years) who were maintained on long-term regular HD therapy mostly via arteriovenous fistulas three times per week in 4-h sessions.

Hypertensive nephropathy was the commonest cause of uremia (n =39), then diabetic nephropathy (n= 27), Glomerulonephritis (n= 11), chronic pyelonephritis (n= 1).

According to **Yigla *et al.*** [7] PH was defined as a systolic PAP> 35 mmHg.

All patients included in this study underwent the following:

(1) A detailed clinical examination included age; sex; smoking habits; associated comorbidity particularly diabetes mellitus (DM) and hypertension; age at time of CKD, etiology of renal failure, duration of dialysis treatment, and dialysis access.

(2) Laboratory investigations included complete blood count (CBC), serum calcium, phosphorus, uric acid, urea, creatinine, and estimated GFR.

(2) Abdominal ultrasonography.

(4) Transthoracic Doppler echocardiography: Every patient underwent a complete two-dimensional and Doppler echocardiography study on the day post dialysis within 4 h after completion of dialysis when the patient had reached the ‘‘dry weight’’ prescribed by nephrologists on the clinical examination including BP and weight in order to avoid overestimation of pulmonary artery pressure (PAP) due to volume overload, Experienced cardiologists performed all examinations using an (Philips IE33, Andover, MA, USA) or (Philips ClearVue 350, USA) ultrasound machine.

The results of TTDE were used to determine PAP, right ventricular function, ejection fraction, and tricuspid regurge.

Systolic PAP: A tricuspid regurgitation systolic jet was recorded from the parasternal or apical window with the continuous- wave Doppler echocardiography probe. Systolic right ventricular (or pulmonary artery) pressure was calculated using the modified Bernoulli equation: PAP = 4. (tricuspid systolic jet) 2 +10 mmHg (estimated right atrial pressure) [8].

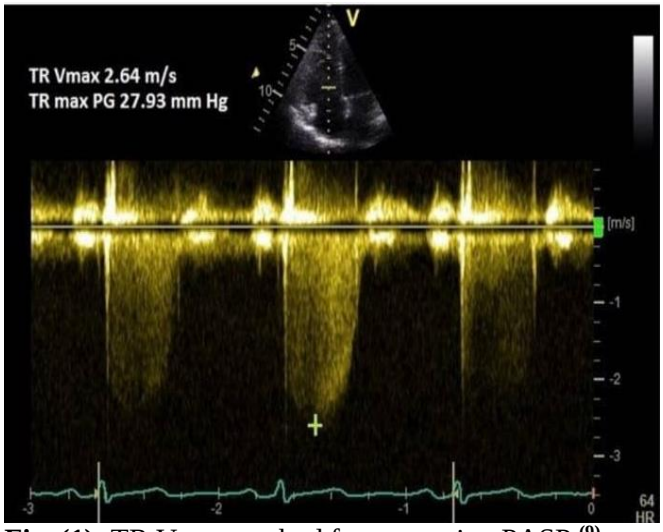

Fig. (1): TR Vmax method for measuring PASP [9].

Statistical analysis

The prevalence of PH was calculated using the SPSS 22 software. CKD patients were evaluated after dividing into those undergoing HD, and not undergoing dialysis, with and without PH Clinical, hemodynamic, and metabolic variables were compared between patients with and without PH with ‘‘t’’ test. Values were expressed as mean± Standard deviation (SD) and as percentage for categorical parameters. Differences between groups were compared with Student’s t-test for parametric continuous variables.

Chi-square test was applied for estimating the occurrence of categorical variables. Person’s correlation coefficient was used to test the relationship between PAP and other parameters. A P value <0.05 was used as the threshold of statistical significance.

RESULTS

The study was conducted among two groups, CKD patients undergo regular HD and CKD patients not on dialysis. A total of 80 patients were enrolled and of which, 40 were not on dialysis (50%) and 40 patients were on dialysis (50 %). 44 males (55%) and 36 females (45%) with mean age of 56.91±16.30.

Table (1): Socio demographic data for whole study group.

		N / Mean	% / SD	Median (IQR)
Group	Non-Dialytic	40	50.0%	
	Dialytic	40	50.0%	
Age (years)		56.91	16.30	58.5 (43 - 70)
Sex	Male	44	55.0%	
	Female	36	45.0%	

Baseline echocardiographic findings of both the groups are summarized in Table 2 and show that among whole study 43 from 80 (53.8%) patients have PH with mean PASP of 37.3±11.08.

Table (2): Transthoracic Doppler echocardiography for whole study group.

		N / Mean	% / SD	Median (IQR)
PASP mmHg		37.3	11.08	35 (29 - 44)
PH	No	37	46.3%	
	Yes	43	53.8%	
EF%		61.18	9.74	61 (56 - 66.5)

Diabetes mellitus and hypertension were the most common etiologies of renal failure in both groups. But DM are more common in Non-Dialytic group 50% of cases and in dialytic group hypertensive cases were more common 65
% of cases (Table 3).

Table (3): Past history of CKD between Non-dialytic and Dialytic groups.

		Group		Mann-Whitney test of sig.	
		Non-Dialytic group	Dialytic group		
		Median (IQR) N (%)	Median (IQR) N (%)	P-Value	Sig.
Duration of CKD (by years)		2 (0.2 - 4)	5 (3.5 - 7)	<0.001	S
Etiology of CKD	Pyelonephritis	1 (2.5%)	0 (0%)	0.013**(F)**	S
	GN	5 (12.5%)	6 (15%)		
	DM	20 (50%)	8 (20%)		
	HTN	14 (35%)	26 (65%)		

(F) Monte Carlo Fisher's Exact test of significance.

There was non statistically significant difference in HB level, serum phosphorous, serum calcium and highly statistically significant increase in serum creatinine and blood urea in dialytic group (Table 4).

Table (4): Lab investigations between Non-dialytic and Dialytic groups.

	Group		Student t-test of sig.	
	Non-Dialytic group	Dialytic group		
	Mean ± SD Median (IQR) N (%)	Mean ± SD Median (IQR) N (%)	P-Value	Sig.
lobin (g/dl)	9.95 ± 2.36	9.71 ± 2.22	0.644	NS
Creatinine (mg/dl)	3.71 ± 0.47	6.78 ± 1.55	<0.001	S
Urea (mg/dl)	111	127.5	0.039	S
Estimated GFR (mL/min/1.73 m^2)	16.96 ± 3.29	9.39 ± 2.02	<0.001	S
Total Ca (mg/dl)	7.95 ± 0.98	8.31 ± 0.92	0.097	NS
Phosphorus (mg/dl)	5.46 ± 1.28	4.97 ± 1.68	0.146	NS

(M) Mann-Whitney test of significance. **(F)** Monte Carlo Fisher's Exact test of significance.

Comparison between both groups regarding echocardiography findings showed is no statistically significant difference between both of them regarding ejection fraction (P value 0.891) and highly statistically significant increase in PH (65%) in dialytic group and mean PASP 41.22±11.32 in dialytic group versus 33.37 ± 9.43 in non-dialytic group (Table 5).

Table (5): Transthoracic Doppler echocardiography between Non-dialytic and Dialytic groups.

		Group		Student t-test of sig.	
		Non-Dialytic group	Dialytic group		
		Mean ± SD N (%)	Mean ± SD N (%)	P-Value	Sig.
PASP mmHg		33.37 ± 9.43	41.22 ± 11.32	0.001	S
PH	No	23 (57.5%)	14 (35%)	0.044	S
	Yes	17 (42.5%)	26 (65%)		
EF%		61.03 ± 10.02	61.33 ± 9.58	0.891	NS

(F) Monte Carlo Fisher's Exact test of significance.

There was positive correlation between PASP and kidney function, CKD duration and no correlation between HB level, calcium, phosphorus dialysis duration.

Table (6): Correlation between PASP and risk factors in the whole study.

Whole group N=80		Age	Duration of CKD (by years)	HB	S.Creat	B.Urea	eGFR	Total Ca
PASP mmHg	Pearson Correlation	-0.205	0.512	-0.244	0.456	0.325	-0.447	0.087
	P-Value	0.068	<0.001	0.029	<0.001	0.003	<0.001	0.44
	Sig.	NS	S	S	S	S	S	NS

Whole group N=80		Phosphorus	Uric Acid	Kidney in ultrasound
PASP mmHg	Pearson Correlation	0.061	-0.09	0.317 **(S)**
	P-Value	0.59	0.427	0.004
	Sig.	NS	NS	S

(S) Spearman's method to correlate between two variables.

Table (7): Correlation between pasp and dialysis duration in the dialytic group.

Dialytic group N=40		Dialysis duration (by years)
PASP mmHg	Pearson Correlation	0.249
	P-Value	0.122
	Sig.	NS

DISCUSSION

This was a cross-sectional study investigating a small number of CKD patients. Patients with CKD and on dialysis were selected to investigate the prevalence and risk factors of PH. Pulmonary hypertension is defined as mean pulmonary arterial pressure (PAP) ≥25mm Hg as measured by right heart catheterization. It is relatively common in patients with CKD and ESRD. The prevalence of PH varies from 18% to 68% in patients on HD [(4)].

Doppler echo with modified Bernoulli equation was done by which PH was considered with PAP ≥35 mm Hg. Using TTDE, measurement of PASP is based on the tricuspid regurgitation jet, a phenomenon that can be recorded in most physiologic and pathologic conditions. In the absence of pulmonary stenosis, PASP is estimated by the calculation of right ventricular systolic pressure by a modified Bernoulli equation and is computed as 4 times the square of maximum tricuspid regurgitation jet velocity (TRV), plus right atrial pressure [(6)].

Increased cardiac output by AVF due to increased sympathetic activity resulting in an increase in myocardial contractility and heart rate, and increased pulmonary blood flow-, anemia, and hypervolemia in patients undergoing dialysis may also increase PAP. Extremely limited studies are available relating to PH in dialysis and nondialysis CKD patients. In this study, we analyzed the prevalence of PH in CKD patients on conservative treatment and on regular HD.

Age is an important factor for the occurrence of PH in dialysis patients with higher incidence in older age group [(10)]. In our study, the mean value of patients age with PH was 48.87 compared to 46.57 in patients without PH. The prevalence of PH varied from 27% to 58% in dialysis patients [(11)].

Our study found no significant difference between gender and development of PH. Similarly, **Tarrass *et al.*** [12] and **Kumbar *et al.*** [13] reported that there was no difference between gender and development of PH.

Severe PH with PAP ≥45–50 mm Hg was seen up to 27.5% in patients on dialysis. We observed that 48.5% of the study population had PH which was high in patients on HD than in nondialysis (59.6% vs. 37.5%, *P* <0.019). This finding was in concurrence with another study of Abdelwhab that showed higher prevalence of PH in dialysis than on conservative treatment [14]. This is in contrast to other studies of **Havlucu *et al.*** [15] **and Tarrass *et al.*** [12] on HD patients where lower rate of prevalence was observed. This may be due to varying definitions for PH in different studies. We also determined risk factors for the development of PH which was found to be directly related to the duration of dialysis [16, 17]**.**

In our study, 42.5% of non-dialytic CKD patients had PH with mean PASP of 33.37±9.43 in comparison with 65% of dialytic group with mean PASP of 41.22±11.32. We don`t have sufficient data on the prevalence of PH in non-dialytic CKD patients. **Yigla *et al.*** [18] reported slight lower in the prevalence of PH (13.7%) in non-dialytic CKD patients. Another study on nondialysis CKD patients also showed similar results with the prevalence of 21.1% and found that old age, anemia, and LV dysfunction were related to increased PAP [19].

We find non-significant decrease in hemoglobin level (P-Value 0.453), in PH subgroup in dialytic group. But, **Yigla *et al.*** [18] reported that the hemoglobin was significantly lower in the PH subgroup which may be explained in CKD according to **Buemi *et al.*** [20] who reported that the association between lower hemoglobin levels and PH may be explained by tissue hypoxia triggered by lower hemoglobin levels may increase PAP.

The current study demonstrated non-significant increase in serum phosphorus level in dialytic group with PH .similarly to **Amin *et al.*** [21] reported that there was no significant difference between patients with PH and those without PH in HD regarding to serum phosphorus. In the other hand **Magdy *et al.*** [22] reported that there is a positive significant correlation between PAP and serum phosphorous.

Amin *et al.* [21] reported that there was no significant difference between patients with PH and those without PH in HD regarding serum calcium and this was against to **Kumbar *et al.*** [13] who reported that the serum calcium level was significantly lower in the patients with PH. This study demonstrated non-significant decrease in serum calcium level.

This study reported no statistically significant difference in systolic function in PH in both groups.

Abdallah *et al.* [23] reported that CKD duration and AVF duration were positively correlated with systolic PAP in patients receiving HD. In contrast, **Amin *et al.*** [21] and **Tarrass *et al.*** [12] reported that there was no significant difference between patients with PH and those without PH as regards to duration of dialysis. In our study also there is no significant difference regarding dialysis duration but we found that PH significantly increase with the increase of CKD duration similar to **Abdallah *et al.*** [23]**.** Data about the role of AVF flow mediated CO elevation in the development of PH is conflicting [7, 24]. In this study, despite a positive correlation between AVF flow and SPAP, multivariate analysis did not show a significant relation between them.

CONCLUSION

It could be concluded that PH is a common finding in CKD patients; the prevalence was highest among patients with ESRD on HD than those on conservative management. Early detection of PH is important to avoid the serious consequences of the disease. Until better understanding of the pathophysiology and effect of interventions such as the use of vasodilator treatments in this population becomes available, there is a call for a consensus involving nephrologists and chest department on how best to screen for, investigate and manage these patients, and a move away from simply labeling the condition as ‘heart failure’.

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