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## The role of parathyroid hormone and cardiac output in pulmonary hypertension in hemodialysis patients

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### ABSTRACT

**Introduction:** High prevalence of pulmonary hypertension has been reported in patients with chronic renal failure, especially those undergoing hemodialysis.

**Objectives:** Considering the high prevalence of pulmonary hypertension in hemodialysis patients and uncertainty about the causes, the present study planned to investigate the role of parathyroid hormone (PTH) and cardiac ejection fraction (EF %) in development of pulmonary hypertension.

**Patients and Methods:** By simple census sampling, all patients on hemodialysis in the hemodialysis center of Birjand University of Medical Sciences were enrolled. After obtaining written consent, the EF% and systolic pulmonary artery pressure (sPAP) were determined using echocardiography (MEDISON V10 model, Korea). The cut-point of less than 35 mm Hg was considered for normal sPAP. The blood sample was prepared to assay PTH using COBAS411 and ROCH kit. Independent t test or Man-Whitney test were used to compare means. *P* value <0.05 was considered significant.

**Results:** A total of 114 patients were enrolled in the study. Finally 89 patients, including 49 (55.1%) male and 40 (44.9%) female completed the study. The mean age and mean sPAP of the studied patients were 55.14 ± 15.68 years and 30.65 ± 12.10 mm Hg respectively. Among the studied patients, normal and high sPAP were reported in 60 (67.4%) and 29 (32.6%) cases respectively. Cardiac EF% in patients with normal and high sPAP was 59.08 ± 2.83 versus 56.37 ± 4.79 respectively (*P* = 0.01). PTH was determined 275.12 ± 218.44 versus 395.67 ± 332.05 (pg/mL) (*P* = 0.03), in patients with normal and high sPAP respectively.

**Conclusion:** The prevalence of pulmonary hypertension in the studied patients was 32.6%. Patients in the pulmonary hypertension group had higher levels of PTH and lower cardiac EF%.

### *Implication for health policy/practice/research/medical education:*

We found that the prevalence of pulmonary hypertension in patients was 32.6%. Patients in the pulmonary hypertension group had higher levels of PTH and lower cardiac EF%.

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### Introduction

High prevalence of pulmonary hypertension has been reported in patients with chronic renal failure, especially in those undergoing hemodialysis (1,2). The incidence of pulmonary hypertension is also high in patients undergoing peritoneal hemodialysis (3). The high prevalence of pulmonary hypertension has been also

reported (up to 56%) in other studies (4,5). Despite numerous studies, there are still many questions about the prevalence and pathogenesis of pulmonary hypertension in dialysis patients (6). Possible mechanisms including oxidative stress induced endothelial dysfunction, chronic inflammation due to frequent contact with dialysis membrane, vascular calcification, and increased flow

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of shunt caused by hemodialysis fistula (7). Secondary hyperparathyroidism has been also considered as an independent factor in the pathogenesis of pulmonary hypertension in patients with chronic renal failure (8). Several studies have not confirmed this hypothesis (7,9).

Cardiac and kidney interaction highlight a bidirectional response, which is known as cardio-renal syndrome, and pulmonary hypertension is a common hemodynamic complication of left ventricular heart failure (10-12).

According to the high prevalence reports of pulmonary hypertension, as well as the high prevalence of secondary hyperparathyroidism and cardiac dysfunction in patients with chronic renal failure, and also according to uncertainty of results from previous studies, the main goal of the present study was to investigate the prevalence and role of parathyroid hormone (PTH) and cardiac ejection fraction (EF%) in development of pulmonary hypertension in patients with chronic hemodialysis.

## Patients and Methods

### Study design

In a descriptive-analytic study, patients undergoing regular hemodialysis (2 to 3 times per week) at the dialysis center of Birjand University of Medical Sciences (in 2018) were selected through simple census sampling. Patients with mitral valve stenosis, clinically advanced left ventricular heart failure, pulmonary embolism in the past, chronic obstructive lung disease, interstitial lung disease and liver failure were excluded. Finally, 114 patients were selected and written consent obtained. Systolic pulmonary artery pressure (sPAP) and EF% were determined using a VIVID 10 echocardiography equipment (MEDISON, Korea). Systolic PAP greater than 35 mm Hg was defined as pulmonary hypertension.

Blood samples were obtained prior to dialysis and were sent to a laboratory to assay the serum levels of calcium, albumin, hemoglobin, urea, creatinine, and alkaline phosphatase. The serum level of intact PTH was determined using COBAS411 equipment and ROCH kit. The PRESTIGE 24i device and Pars Azmoon kits were used to measure serum high-sensitivity C-reactive protein (hs-CRP) levels.

### Ethical issues

The ethical committee of Birjand University of Medical Sciences (Ethical Code# Ir.bums.REC.1396.156) approved the study. The informed consent was taken from the participants.

### Statistical analysis

The data were analyzed by SPSS software version 23. Kolmogorov-Smirnov test was used to determine normal distribution of the data. Man-Whitney and Independent

*t* tests were used to compare means with abnormal and normal distribution respectively. *P* value less than 0.05 was considered statistically significant.

## Results

From 114 participated patients, finally 89 patients including 49 (55.1%) males and 40 (44.9%) females were enrolled in the study. The studied parameters were compared between males and females and presented in Table 1. Hemodialysis sessions were conducted three times per week for 59 (66.3%), two times per week for 29 (32.6%) and once times per week for one patient (1.1%). The duration of hemodialysis was 4 hours for each session. The history of hemodialysis was on average  $30.37 \pm 29.18$  months for patients (Table 1).

The mean of sPAP and EF% for all patients were  $30.65 \pm 12.10$  mm Hg and  $58.20 \pm 3.78\%$ , respectively. Systolic PAP more than 35 mm Hg (pulmonary hypertension group) was recorded in 29 (32.6%) and less than 35 mm Hg (NPH; non-pulmonary hypertension group) in 60 (67.4%) cases of the studied patients. The mean of sPAP in the pulmonary hypertension group and the NPH group was  $44.65 \pm 6.25$  mm Hg and  $23.88 \pm 7.55$  mm Hg, respectively.

There were 74 patients (83%) with  $EF > 52\%$  and 15 patients (17%) with  $EF < 52\%$ . Mean of EF% in the NPH group versus pulmonary hypertension group was  $59.08\% \pm 2.83\%$  and  $56.37\% \pm 4.79\%$  respectively ( $z = -3.14$  and  $P = 0.002$ ; Table 2). Mean of sPAP was  $28.68 \pm 10.74$  mm Hg and  $40.33 \pm 14.07$  mm Hg in patients with  $EF > 52\%$  versus  $EF < 52\%$  respectively ( $z = -2.98$ ,  $P = 0.002$ ). Mean of intact PTH serum level in the NPH group compared to the pulmonary hypertension group was  $278.12 \pm 218.44$  pg/mL and  $395.67 \pm 332.05$  pg/mL, respectively ( $z = -2.10$  and  $P = 0.03$ ; Table 2).

## Discussion

The mean of sPAP for all patients under the study was  $30.65 \pm 12.10$  mm Hg. By definition, the sPAP in the range of 30 to 35 mm Hg is considered normal (13). Diagnostic evaluations are needed in the condition of sPAP > 40 mm Hg. Accordingly, the prevalence of pulmonary artery hypertension in the present study was 32.6% and the mean of sPAP in patients of the pulmonary hypertension group was  $44.65 \pm 6.25$  mm Hg.

According to the World Health Organization (WHO) classification, kidney failure is among the miscellaneous causes of pulmonary hypertension (6). Kidney failure may independently cause structural changes in pulmonary vessels and pulmonary hypertension. These changes are proportional to severity of kidney failure, and despite the onset of a regular dialysis schedule, its progression is not stopped (14). The prevalence of pulmonary hypertension

**Table 1.** Comparison of studied parameter between male and female

Parameter	Mean± SD	Male, 49 (55.1%)	Female, 40 (44.9%)	P value
Age (y)	55.14±15.68	54.48±16.29	55.95±15.06	Z=-0.36, P=0.71
Pulmonary pressure (mm Hg)	30.65±12.10	29.55±13.44	32.00±10.24	Z=-1.06, P=0.28
Weight (kg)	62.25±13.02	65.71±13.37	58.02±11.36	Z=-2.60, P=0.00
Dialysis duration (mon)	30.37±29.18	29.40±32.81	31.55±24.38	Z=-0.85, P=0.39
Dialysis frequency per week	2.65±0.50	2.65±0.48	2.65±0.53	Z=-0.13, P=0.89
Calcium (mg/dL)	8.70±1.11	8.53±1.11	8.90±1.10	Z=-0.95, P=0.33
Alkaline phosphatase (Unit/L)	297.76±191.24	265.93±120.36	336.75±248.72	Z=-1.84, P=0.06
hs-CRP (mg/L)	15.68±13.87	17.65±13.59	13.27±13.99	Z=-2.51, P=0.01
Parathyroid hormone (pg/mL)	314.40±265.15	328.95±255.45	296.58±278.79	Z=-0.94, P=0.34
Serum urea (mg/dL)	132.16±34.16	132.69±37.40	131.52±30.17	T=0.16, P=0.87
Serum creatinine (mg/dL)	7.20±2.36	7.64±2.63	6.65±1.89	T=1.99, P=0.04
Albumin (g/dL)	3.86±0.37	3.90±0.34	3.80±0.41	Z=-0.85, P=0.39
Phosphorus (mg/dL)	5.28±1.16	5.28±1.32	5.28±0.93	Z=-0.26, P=0.87
Hemoglobin (g/dL)	11.16±1.34	11.33±1.39	10.95±1.27	T=1.34, P=0.18
Cardiac ejection fraction (%)	58.20±3.78	58.16±3.91	58.25±3.67	Z=-0.08, P=0.93
Calcium-phosphorus product (mg <sup>2</sup> /dL <sup>2</sup> )	46.14±12.64	45.21±13.46	47.27±11.64	Z=-0.89, P=0.37

**Table 2.** Comparison of studied parameter in non-pulmonary hypertension and pulmonary hypertension groups

Parameter	PAP ≥ 35 mm Hg	PAP < 35 mm Hg	z or t	P value
Number of patients	29	60		
Age (y)	52.37±17.73	56.48±14.55	z=-0.74	0.45
Dialysis duration (mon)	36.86±34.03	27.23±26.27	z =-0.74	0.49
Dialysis frequency per week	2.72±0.45	2.61±0.52	z =-0.88	0.37
Ejection fraction%	56.37±4.79	59.08±2.83	z=-3.14	0.002
Alkaline phosphatase (U/L)	269.71±78.76	310.16±233.77	z=-0.05	0.95
Parathyroid hormone (pg/mL)	395.67±332.05	275.12±218.44	z=-2.10	0.03
Serum calcium (mg/dL)	9.03±0.99	8.54±1.14	z=-1.85	0.06
Serum urea (mg/dL)	127.75±28.11	134.30±36.75	t=0.84	0.4
Serum creatinine (mg/dL)	6.78±1.81	7.40±2.58	t=1.14	0.25
Serum albumin (g/dL)	3.83±.38	3.87±.37	z =-0.28	0.77
Hemoglobin (g/dL)	11.05±1.27	11.61±1.39	t =0.50	0.61
Calcium-phosphorus product (mg <sup>2</sup> /dL <sup>2</sup> )	48.12±8.62	45.18±14.15	z=-1.50	0.13

in patients with kidney failure and patients on dialysis is diverse and in several studies reported up to 56% (4, 5). Although pulmonary hypertension is more common in hemodialysis patients, the incidence is also high in patients on continuous ambulatory peritoneal dialysis (3, 5).

In comparison with normal pulmonary artery pressure group in the present study; PTH levels were found to be significantly higher in the pulmonary hypertension group. Hyperparathyroidism is a common phenomenon in patients with renal failure (15). Parallel relationship has been reported between hyperparathyroidism and

pulmonary hypertension in patients with renal failure (8). A study conducted by Zhang and colleagues showed that PTH and body mass index are important risk factors in the development of pulmonary artery hypertension in patients with renal failure (16); however, there is some evidence against this hypothesis (7,9). A possible mechanism could be calcium deposits in the vascular wall (17). Calcium-phosphorus product over than 70 mg<sup>2</sup>/dL<sup>2</sup> is considered not only as an important factor in ectopic calcification and calcific uremic arteriolopathy in patients with renal failure but also as the only factor

(18). In fact, the calcification phenomenon is affected by primary or secondary hyperparathyroidism (19). In the present study, calcium-phosphorus product was found to be  $48.12 \pm 8.62 \text{ mg}^2/\text{dL}^2$  in the pulmonary hypertension group, which declared slightly higher (but not statistically significant) in comparison with the NPH group. Contrary to the results of our study, in a study by Suresh et al on 108 patients with chronic renal failure, it was concluded that patients with higher calcium  $\times$  phosphorus product had significantly higher pulmonary artery pressure (14).

Furthermore, Wilmer and Magro detected that vascular damage occurs in the early stages of kidney failure and even much earlier than uremia arteriopathic calcification, while this phenomenon is affected by various factors such as hyperparathyroidism, vitamin D intake, calcium intake and calcium-phosphorus product and also blood phosphorus levels (20).

The present study was also showed that pulmonary artery pressure could be affected by EF% in hemodialysis patients. We found that patients with pulmonary hypertension had lower EF% and also patients with lower EF% had higher sPAP. In accordance with the findings of our study, Suresh et al have found similar results in their study (14). Fabbian et al stated that pulmonary hypertension in patients with renal failure undergoing peritoneal dialysis or hemodialysis is associated with a lower EF % (5). Accordingly, Sarnak et al showed that multivariable analyses indicate that low-cardiac output is one of the causes leading to pulmonary hypertension in patients with renal failure (21). Additionally, Genctoy et al indicated that patients with pulmonary hypertension had higher levels of PTH, lower hemoglobin, and lower cardiac output (8).

### Conclusion

Pulmonary hypertension is a common phenomenon in patients with chronic renal failure undergoing hemodialysis. Although several factors contribute to this complication, hyperparathyroidism and the reduction of cardiac output are essentially contributed to the development of pulmonary hypertension in patients undergoing chronic hemodialysis.

### Limitation of the study

The most important limitation of the study was inevitably administration of calcium and vitamin D supplements. These supplements can affect PTH secretion.

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### Authors' contribution

SGMM and ZS designed the study, observed accuracy and validity of the study. The manuscript was written by SGMM. MG and NA collected the data and followed up with the study. AAR conducted the statistical analysis. All authors read and revised the final manuscript.

### Conflicts of interest

There are no competing interests to declare

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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