IJKD DIALYSIS

Correlation Between Fibroblast Growth Factor-23 and Pulmonary Arterial Hypertension in Hemodialysis Patients

Maryam Miri,[1] Mahnaz Ahmadi,[2] Mohsen Hatami[2]

[1]Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Mashhad University of Medical Sciences, Mashhad, Iran

Original Paper

Keywords. fibroblast growth factor23, pulmonary wedge pressure, pulmonary artery hypertension, renal dialysis

Introduction. Pulmonary artery hypertension (PAH) is common in end stage renal disease (ESRD) patients undergoing hemodialysis. Fibroblast growth factor-23 (FGF-23) increases in hemodialysis but its relationship with PAH is not completely understood. The aim of this study was to evaluate the relation between FGF-23 level and development of PAH in ESRD patients undergoing hemodialysis.
Methods. Patients undergoing hemodialysis for more than 6 months were enrolled in this cross-sectional study. Transthoracic echocardiography was performed to measure ejection fraction and pulmonary artery pressure (PAP) in all patients. Patients were grouped into normal PAP (PA*P* < 25 mmHg), elevated PAP (25 < PA*P* < 35 mmHg) and PAH (PA*P* > 35 mmHg). Parathormone hormone, calcium, phosphorus, vitamin D, and hemoglobin levels were also evaluated.
Results. Eighty-five patients (48 male, 56.47%) enrolled in this study. The mean age of the patients was 51.05 ± 16.45 years. Most of the patients (49, 57.65%) had normal PAP, 20 (23.53%) had elevated PAP and 16 (18.82%) had PAH. Serum biochemical markers and demographic characteristics were not significantly related to different PAP values ($P > .05$). Most of the patients (42, 49.41%) had normal FGF-23 levels. There was a significant relationship between PAP groups and FGF-23 and parathormone levels, $P < .001$, and $P < .05$; respectively. FGF-23 was significantly higher in PAH and elevated PAP groups compared with normal PAP group ($P < .05$). Only a significant positive correlation was observed between FGF-23 levels and PAP ($P < .001$).
Conclusion. This finding highlights the possible role of FGF-23 in the development of vascular complications in ESRD patients.

IJKD 2021;15:300-5
www.ijkd.org

INTRODUCTION

The risk of developing cardiovascular diseases (CVD) is high among patients with end-stage renal disease (ESRD) who undergo chronic dialysis.[1] The cardiovascular system undergoes various functional and structural changes along with the decline in kidney function.[1] These changes in cardiovascular system occur to overcome the circulatory insufficiency.[1] The main cardiovascular changes following chronic kidney disease include left ventricular hypertrophy accompanied by systolic or diastolic dysfunction.[1] Moreover, cardiovascular dysfunction is accelerated by the development of vascular complications including arteriosclerosis and atherosclerosis.[1] Pulmonary artery hypertension (PAH) is among the common cardiovascular complications that often coexists with chronic kidney disease.[2] It has been demonstrated that the development of PAH is related to the duration of dialysis. PAH is commonly seen in

patients undergoing dialysis for more than 5 months.[3] Despite the direct relationship between the incidence of PAH and stage of chronic kidney disease, the exact mechanism behind this relation is not clearly understood.[2] PAH is associated with intimal thickening, and medial hypertrophy of distal pulmonary arteries that increase the pulmonary vascular pressure and disrupt right ventricular function.[4,5] Metabolic abnormalities are among the suggested pathologies for the development of PAH.Metabolic abnormalities are considered as new emerging factors which are correlated with patient outcome and treatment response.[6,7] Fibroblast growth factor-23 (FGF-23) is one of these metabolic factors which is mostly secreted from osteocytes regulating the serum phosphate level.[7] Moreover, FGF-23 regulates calcium balance, vitamin D activation, and the expression of parathyroid hormone (PTH).[7] In healthy subjects, sectretion of FGF-23 and PTH is induced by increased serum phosphate levels. However, the level of FGF-23 changes in different clinical contexts and is now believed to be involved in the progression of various diseases.[8] In kidneys, FGF-23 signals renal phosphate reabsorption reduction and therefore decreases serum phosphate levels.[7] Therefore, FGF-23 concentration increases with the impairment of kidney function and gradual decline in glomerular filtration rate (GFR) in patients with chronic kidney disease.[7] It has been demonstrated that patients undergoing hemodialysis have extremely elevated FGF-23 levels.[9] However, increased level of FGF-23 may have an inverse effect on cardiovascular system.[9] Increased level of FGF-23 is associated with many cardiovascular diseases including left ventricular hypertrophy (LVH) and reduced left ventricular ejection fraction (LVEF) in hemodialysis patients.[9] It has been hypothesized that the FGF-23 might be a burden to heart failure and vascular remodeling in pulmonary arteries in PAH patients.[8] However, the relation between FGF-23 serum level and the development of PAH is still unclear. Therefore, in the present study, we aimed to evaluate the relation between FGF-23 level and development of PAH in ESRD patients undergoing hemodialysis.

MATERIALS AND METHODS

The present cross-sectional study was approved by the Mashhad University of Medical Sciences Ethics committee and took place in Montaserieh Hospital, Mashhad, Iran; from Jan 2017 to Jan 2019. Every patient who was undergoing hemodialysis for more than 6 months enrolled in the present study after signing an informed consent. Patients who had a history of left ventricular failure, asthma, obstructive sleep apnea, chronic obstructive lung disease (COPD) or interstitial lung disease (ILD), or increased pulmonary artery pressure (PAP) due to rheumatoid diseases, chronic blood clots (CTEPH) were excluded.

All patients underwent transthoracic echocardiography and PAP as well as ejection fraction values were documented. Patients were grouped into three groups based on their PAP as follows: 1) normal PAP (PAP < 25 mmHg), 2) elevated PAP (25 < PAP < 35 mmHg), and 3) PAH (PAP > 35 mmHg). Serum FGF-23, parathyroid hormone, calcium, phosphorus, vitamin D, and hemoglobin levels were documented for all patients.

Correlation between the study variables including FGF-23 and PAH was evaluated using the Pearson correlation coefficient. Parametric tests were used for the comparison of the study variables between study groups.The SPSS software (version 20) was used for the analysis of the study data and $P < 0.05$ was considered as statistically significant.

RESULTS

A total number of 85 patients enrolled in the present study. Most of the patients were male (48, 56.47%) and the mean (standard deviation) age of the study population was 51.05 (16.45) years. The demographic and laboratory findings of the study population are summarized in Table 1. Among the study population, most of the patients had normal PAP (49, 57.65%) while 20 patients (23.53%) had abnormal PAP and the rest of the study population (16, 18.82%) had PAH. Distribution of PAP categories among the study population is demonstrated in Table 2. There was no significant relationship between different PAP values and patients demographic data (Table 2). Moreover, PAP was not related to arteriovenous fistula or age (P > .05). Similarly, serum biochemical markers were not related to the different PAP volumes (P > .05).

Most of the patients (42, 49.41%) had normal FGF-23 levels. Low and high levels of FGF-23 were observed in 6 (7.06%) and 37 patients (43.53%), respectively. Moreover, the entire study population

Table 1. Distribution of Study Population Characteristics

Variables	Frequency	Percent
Male Gender	48	56.47
Female Gender	37	43.53
Diabetes	26	30.59
Hypertension	18	21.18
Right Arteriovenous Fistula	77	90.59
Left Arteriovenous Fistula	8	9.41
Laboratory Data	**Mean**	**Standard Deviation**
Calcium	8.71	0.88
Phosphor	5.55	0.86
Albumin	3.93	0.38
Parathormone	493.32	412.57
Vitamin D	38.12	15.16
Alkaline Phosphatase	386.33	171.90
Hemoglobin	11.05	1.37
Ejection Fraction	54.45	4.24
Pulmonary Artery Pressure	29.51	11.21
FGF-23	182.36	208.73

had elevated serum PTH. There was a significant relationship between PAP categories and both FGF-23 and PTH levels ($P < .001$ and $P < .05$, respectively; Table 3). The Games-Howell test demonstrated that the mean FGF-23 in patients with PAH and elevated level of PAP was significantly greater than those with normal PAP ($P < .05$). Moreover, the same statistical test revealed that PTH level was significantly higher in patients who had PAH in contrast to those with elevated levels of PAP ($P < .05$). The Pearson correlation coefficient analysis showed that among the plasma biochemical markers, only FGF-23 level was positively correlated with PAP ($P < .001$).

DISCUSSION

Among the clinical and laboratory variables studied in the present study, only FGF-23 and serum parathormone hormone levels were related to the development of PAH and PAH patients had increased FGF-23 levels.

CVDs are among the common complications of chronic kidney disease and account for considerable mortality in this group of patients especially those undergoing dialysis.[10] PAH is one of the cardiovascular complications of chronic kidney disease. PAH has a progressive nature and directly decreases the survival of patients

Table 2. The Relation Between Different Groups of Pulmonary Artery Pressure and Study Variables

Variable	Pulmonary artery pressure						*P*
	Normal		Elevated		Hypertension		
	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Male	27	55.10	11	55	10	62.50	> .05
Female	22	44.90	9	45	6	37.50	
Diabetes	16	32.65	5	25	5	31.25	
Hypertension	10	20.41	4	20	4	25.00	> .05
Diabetes and Hypertension	5	10.20	3	15	2	12.50	
Arteriovenous Fistula (Left)	45	91.84	17	85	15	93.75	> .05
Arteriovenous Fistula (Right)	4	8.16	3	15	1	6.25	

Table 3. The Relation Between Different Pulmonary Artery Pressure Groups and Serum Biochemical Markers

Variables	Pulmonary Artery Pressure						*P*
	Normal		Elevated		Hypertension		
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Calcium	8.74	0.94	8.75	0.81	8.56	0.81	> .05
Phosphorus	5.57	0.94	5.33	0.64	5.78	0.78	> .05
Albumin	3.95	0.36	3.81	0.40	4.01	0.42	> .05
Vitamin D	36.65	15.53	37.80	11.27	43.00	17.91	> .05
Alkaline Phosphatase	397.65	172.65	337.05	129.68	413.25	210.65	> .05
Hemoglobin	11.00	1.45	11.01	0.98	11.24	1.59	> .05
FGF-23	68.57	92.16	287.90	163.00	398.94	275.61	< .001
Parathormone	492.59	404.99	330.35	256.08	699.25	514.44	< .001
Ejection Fraction	53.78	3.61	55.15	4.79	55.63	5.11	> .05
Vitamin D	36.65	15.53	37.80	11.27	43.00	17.91	> .05
Alkaline Phosphatase	397.65	172.65	337.05	129.68	413.25	210.65	> .05
Hemoglobin	11.00	1.45	11.01	0.98	11.24	1.59	> .05

undergoing hemodialysis.[11] The prevalence of PAH varies among different studies and is reported to reach 58.6% in hemodialysis patients.It has been reported that patients undergoing hemodialysis are more likely to develop PAH compared with those undergoing peritoneal dialysis.[12,13]

Although our study failed to determine clinical or laboratory factors that affect the development of PAH in hemodialysis patients, other studies proposed some risk factors. Mukhtar *et al.* reported a high prevalence of PAH in hemodialysis patients (56%) and demonstrated that arteriovenous shunts had been related to the development of unexplained PAH in ESRD patients.[14] Moreover, in contrast to our study, they demonstrated that female patients were more likely to develop PAH. Other studies with smaller sample size demonstrated similar findings to the findings of the study by Mukhtar *et al.*[14-16] The definition of PAH and duration of dialysis in different populations are the major factors that complicate the comparison of studies on PAH. Although the development of PAH is directly related to the duration of ESRD and dialysis as well as cardiovascular disease history, certain studies demonstrated that some patients may develop early-onset PAH.[13, 14, 17] Similar to the findings of our study, the study by Alhamad *et al.* demonstrated that serum calcium, hemoglobin, and patients' age were not related to the development of PAH.[18]

Regardless of the controversial risk factors in different studies, some novel metabolic biomarkers, including FGF-23 and PTH, are thought to play a role in the pathogenesis of PAH in hemodialysis patients. Although the exact mechanism behind the development of PAH is not clearly understood, it seems that PAH is complicated and multifactorial[15]. The elevated level of FGF-23 has been linked to adverse outcomes in both healthy individuals and chronic kidney disease patients.[19, 20] However, it is still not clearly understood whether the cardiovascular consequences of dysregulated FGF-23 are independent of its mineral metabolism.[21] Fyfe-Johonson *et al.* demonstrated that increased FGF-23 level had been related to the development of hypertension in middle-aged patients after five years of follow-up.[21] They demonstrated that patients who had FGF-23 levels above 60.6 had been more likely to develop hypertension regardless of their kidney function and other cardiovascular risk factors. Moreover, chronic kidney disease patients who had FGF-23 levels above 35 had been more likely to develop PAH.[21] Furthermore, Arnlov *et al.* suggested that FGF-23 above 60 along with micro- and macro-albuminuria were related to increased risk of cardiovascular accidents.[22] Wolf *et al.* demonstrated that the rate of cardiovascular incidents was greater in patients with an increased level of FGF-23.[23] They also suggested FGF-23 as an off-target and a direct toxin for cardiac tissue that causes cardiovascular end-organ damages leading to adverse cardiovascular outcomes in chronic kidney disease patients.[23]

Our study demonstrated that PAH patients have an increased level of FGF-23. This finding was similar to the study by El-Adawy *et al.*[24] Therefore, we may hypothesize that diminished kidney function in hemodialysis patients may not respond properly to FGF-23 levels.[24] Moreover, the increased level of FGF-23 may not be effective enough in advanced renal insufficiency. In the earlier stages of chronic kidney disease in hemodialysis patients, the increased serum level of FGF-23 may not regulate the phosphate level properly.[24] El-Adawy *et al.* suggested that four factors, including serum calcium, vitamin D, iPTH, and systolic blood pressure, regulate FGF-23. Similar to El-Adawy *et al.*, we demonstrated that the PTH level was also correlated with the development of PAH. However, in contrast to El-Adawy *et al.*, we could not find a negative correlation between FGF-23 levels and serum vitamin D and calcium.[24] Other studies including a study by Amin *et al.* suggested that PAH might not be related to PTH level or other metabolic abnormalities.[15] Their study demonstrated that pulmonary artery calcification and secondary hyperparathyroidism may not be the underlying causes of PAH in hemodialysis patients.[15] Hsu *et al.* demonstrated that LVH was prevalent in hemodialysis patients. Furthermore, they reported that FGF-23 was elevated in hemodialysis patients and the FGF-23 level was independently correlated with the development of PAH.[25] They also demonstrated that FGF-23 level was not related to mortality rate after 2 years of follow up in hemodialysis patients with LVH.[25]

One of the limitations of our study was not considering confounders including LVEF and duration of dialysis, as LVEF might increase PAP or induces PAH. This was due to the insufficient

sample size for performing analysis of covariance. Therefore, it is recommended for further studies to evaluate the confounding variables in assessing the relationship between PAP and FGF-23.Another confounding factor might be physical activity levels of the patients. It was previously shown that physical training could affect PTH levels but not FGF-23 in hemodialysis patients.[26] The physical activity of the patients was not assessed in the current study but based on the previous study, it might be a reason for the non-significant findings regarding PTH. There is a need for further studies to assess the effects of physical activity level and PTH on PAH in hemodialysis patients.

CONCLUSION

The present study demonstrated that about half of the patients receiving hemodialysis have elevated PAP or PAH. The FGF-23 serum level was significantly related with PAP. Although the PAH in hemodialysis patients is a multifactorial disorder, our findings highlight the possible role of FGF-23 in the development of vascular complications in patients with end-stage renal disease.

REFERENCES

1. Wanner C, K Amann, T Shoji. The heart and vascular system in dialysis. The Lancet. 2016; 388(10041):276-84.
2. Li Z, X Liang, S Liu, et al. Pulmonary hypertension: epidemiology in different CKD stages and its association with cardiovascular morbidity. PloS one. 2014; 9(12):e114392.
3. Afzal A, MA Bhatti, SJJCPSP Manzoor. Pulmonary hypertension: An emerging problem in patients undergoing regular hemodialysis. 2018; 28:594-6.
4. Tuder RM, JC Marecki, A Richter, I Fijalkowska, SJCicm Flores. Pathology of pulmonary hypertension. 2007; 28(1):23-42.
5. Tan Z, G Ke, J Huang, et al. Effects of Carvedilol on Cardiovascular Events and Mortality in Hemodialysis Patients, A Systematic Review and Meta-Analysis. Iranian journal of kidney diseases. 2020; 14(4):256-66.
6. Samareh Fekri M, A Etminan, A Rashidnedjad, A Mojibian, Y Masoomi. Serum Apelin Peptide Level in Hemodialysis Patients With Pulmonary Arterial Hypertension. Iranian journal of kidney diseases. 2018; 12(4):209-14.
7. Jüppner H. Phosphate and FGF-23. Kidney international Supplement. 2011; 79(121):S24-7.
8. Bouzina H, R Hesselstrand, G Rådegran. Higher plasma fibroblast growth factor 23 levels are associated with a higher risk profile in pulmonary arterial hypertension. 2019; 9(4):2045894019895446.
9. Nielsen TL, LL Plesner, PE Warming, OH Mortensen, KK Iversen, JGJn Heaf. FGF23 in hemodialysis patients is associated with left ventricular hypertrophy and reduced ejection fraction. 2019; 39(3):258-68.
10. Collins AJ. Cardiovascular mortality in end-stage renal disease. The American journal of the medical sciences. 2003; 325(4):163-7.
11. Yigla M, O Fruchter, D Aharonson, et al. Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients. Kidney international. 2009; 75(9):969-75.
12. Mahdavi-Mazdeh M, S Alijavad-Mousavi, H Yahyazadeh, M Azadi, H Yoosefnejad, Y Ataiipoor. Pulmonary hypertension in hemodialysis patients. Saudi journal of kidney diseases and transplantation: an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2008; 19(2):189-93.
13. Fabbian F, S Cantelli, C Molino, M Pala, C Longhini, F Portaluppi. Pulmonary hypertension in dialysis patients: a cross-sectional italian study. International journal of nephrology. 2010; 2011:283475.
14. Mukhtar KN, S Mohkumuddin, SN Mahmood. Frequency of pulmonary hypertension in hemodialysis patients. Pakistan journal of medical sciences. 2014; 30(6):1319-22.
15. Amin M, A Fawzy, MA Hamid, A Elhendy. Pulmonary hypertension in patients with chronic renal failure: role of parathyroid hormone and pulmonary artery calcifications. Chest. 2003; 124(6):2093-7.
16. Havlucu Y, S Kursat, C Ekmekci, et al. Pulmonary hypertension in patients with chronic renal failure. Respiration; international review of thoracic diseases. 2007; 74(5):503-10.
17. Harp RJ, SW Stavropoulos, AG Wasserstein, TW Clark. Pulmonary hypertension among end-stage renal failure patients following hemodialysis access thrombectomy. Cardiovascular and interventional radiology. 2005; 28(1):17-22.
18. Alhamad EH, M Al-Ghonaim, HF Alfaleh, JP Cal, N Said. Pulmonary hypertension in end-stage renal disease and post renal transplantation patients. Journal of thoracic disease. 2014; 6(6):606-16.
19. Lutsey PL, A Alonso, E Selvin, et al. Fibroblast growth factor-23 and incident coronary heart disease, heart failure, and cardiovascular mortality: the Atherosclerosis Risk in Communities study. Journal of the American Heart Association. 2014; 3(3):e000936.
20. Isakova T, H Xie, W Yang, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. Jama. 2011; 305(23):2432-9.
21. Fyfe-Johnson AL, A Alonso, E Selvin, et al. Serum fibroblast growth factor-23 and incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study. Journal of hypertension. 2016; 34(7):1266-72.
22. Ärnlöv J, AC Carlsson, J Sundström, et al. Higher fibroblast growth factor-23 increases the risk of all-cause and cardiovascular mortality in the community. 2013; 83(1):160-6.
23. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. Kidney international. 2012; 82(7):737-47.
24. EL-Adawy N, A Helmy, T Ismail, A Tawfik, HJJCEC

Keryakos. Fibroblast growth factor-23: A possible cause of pulmonary hypertension and left ventricle hypertrophy in hemodialysis patients. 2016; 7(449):2.

25. Hsu HJ, M-S Wu. Fibroblast Growth Factor 23: A Possible Cause of Left Ventricular Hypertrophy in Hemodialysis Patients. The American journal of the medical sciences. 2009; 337(2):116-22.
26. Fakhrpour R, H Hamid Tayebi Khosroshahi, K Ebrahim, et al. Effect of Sixteen Weeks Combined Training on FGF-23, Klotho, and Fetuin-A Levels in Patients on Maintenance Hemodialysis. Iranian journal of kidney diseases. 2020; 14(3):212-8.

Correspondence to:
Maryam Miri, MD
Kidney Transplantation Complications Research Center,
Mashhad University of Medical Sciences, Mashhad, Iran
E-mail: marmar_m59@yahoo.com

Received January 2021
Revised March 2021
Accepted May 2021