Prevalence of pulmonary hypertension in patients with early stages of chronic renal disease

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Abstract
Objective: Pulmonary hypertension (PHT) has recently been described as a cardiovascular complication of chronic kidney disease (CKD). There are many studies on the prevalence of PHT in patients undergoing hemodialysis (HD); however, there are no data on the presence or prevalence of PHT in patients with early-stage kidney disease.

Material and Method: The demographic and laboratory findings for 172 adult patients with stage 1-5 CKD, as well as Doppler echocardiographic findings were evaluated. Systolic pulmonary arterial pressure (sPAP) was compared according to CKD stage, and also between the patients in stages 1-4 and those in stage 5 with and without AVF.

Results: Mean age of the patients was 55.4±15.2 years. Mean sPAP in the entire study group was 34.5±5.7 mmHg and PHT was noted in 90 (52.3%) patients. Mean sPAP and the prevalence of PHT were similar in the stage 1-4 patients and stage 5 patients, regardless of HD (p=0.86). The serum calcium level was significantly lower and the serum intact parathyroid hormone level was significantly higher in patients with PHT than in those without PHT (p=0.02, and p=0.03).

Conclusion: The present findings show that the prevalence of PHT in patients with early stage CKD was similar to those with stage 5 CKD. Due to the high morbidity and mortality rates associated with PHT, follow-up of sPAP via Doppler echocardiography might be indicated in all patients with CKD.

Keywords: Chronic kidney disease, pulmonary hypertension, prevalence

Introduction
Pulmonary hypertension (PHT) is a serious cause of morbidity and mortality, regardless of its etiology. Elevated pulmonary arterial pressure (PAP) can be observed secondary to heart, lung, or systemic disorders (1). PHT, defined as systolic pulmonary artery pressure (sPAP) ≥35 mmHg at rest as estimated via Doppler echocardiography, has been reported with variable prevalence’s in patients with chronic kidney disease (CKD), both predialysis and during hemodialysis (HD) (2). According to Dana Point classification, CKD combined with dialysis is causes of PHT not clear (3).

PHT was first described in a group of HD patients in 1996, after that time many studies have investigated the prevalence of PHT in CKD patients. The prevalence of PHT ranges from 9-39% in cases of non-dialysis-dependent CKD stage 5 patients, 18.8-68.8% in regular HD patients, and 0-42% in peritoneal dialysis patients, but there are no data on the prevalence of PHT in patients with stage 1-4 CKD (4). As such, the present study aimed to determine the prevalence of PHT via Doppler echocardiography in patients with early-stage (stage 1-4) CKD and the factors associated with PHT.

Material and Methods
Patient selection
The study included 172 stage 1-5 CKD patients that regularly received treatment between January 2013 and January 2014 at Balikesir Ataturk State Hospital, Clinic of Nephrology, Balikesir, Turkey. CKD was defined as kidney damage or a glomerular filtration rate (GFR) <60 mL min⁻¹ 1.73 m⁻² for ≤3
The study included 172 CKD patients. Mean age of the patients was 55.4±15.2 years, and 78 (45.3%) were female and 94 (54.7%) were male. In all, 36 (21%) patients were stage 1 and 2, 44 (26%) were stage 3, 38 (22%) were stage 4, and 54 (31%) were stage 5. Among the stage 5 patients, 30 were undergoing HD and 24 were not. Patient clinical characteristics and laboratory findings are summarized in Table 1. The patients’ primary renal diseases varied; 42 (25%) had hypertensive glomerulosclerosis, 34 (20%) had diabetic nephropathy, 28 (16%) had autosomal dominant polycystic kidney disease, 20 (12%) had tubulointerstitial nephritis, 12 (7%) had glomerulonephritis/nephrotic syndrome, 12 (7%) had undergone renal transplantation, and 24 (14%) had an unknown etiology. Mean sPAP in the entire study population was 34.5±5.7 mmHg.

sPAP and the prevalence of PHT did not differ significantly according to disease stage (p>0.05). In addition, sPAP and the prevalence of PHT did not differ between the stage 1-4 patients and stage 5 patients (34.2±6 mmHg and 35.2±4.8 mm Hg, respectively, and 50.8% and 55.6%, respectively; p>0.05). To estimate the effect of an AVF on PHT, stage 5 CKD patients with and without an AVF were compared. All patients with an AVF were undergoing HD. PHT was diagnosed in 16 (53.3%) patients with stage 5 CKD that were undergoing HD and in 14 (58.3%) stage 5 CKD patients not undergoing HD (p>0.05); mean sPAP did not differ significantly between these 2 patient subgroups (34.5±5.3 mmHg vs. 36±6.3 mmHg respectively, p>0.05) (Table 2).

In total, PHT was diagnosed in 90 (52.3%) patients via echocardiography. There weren’t any significant differences in age, gender, systolic and diastolic blood pressure, or the hemoglobin concentration between the patients with and without PHT. The serum Ca level was significantly lower and the serum iPTH level was significantly higher in the patients with PHT than in those without PHT (8.8±1 mg dL-1 vs. 9.3±0.6 mg dL-1 (p=0.02), and 133.5 pg mL-1 vs. 79.6 pg mL-1 (p=0.03), respectively). On the other hand, the prevalence of hypertension was significantly lower in the patients with PHT than in those without PHT (p=0.03). PHT-related data are shown in Table 3. There wasn’t an association between the prevalence of PHT and the etiology of the primary renal disease.

Discussion

To the best of our knowledge, the present study is the first to determine the prevalence of PHT in patients with early-stage CKD. The present findings show that 52.3% of the patients with stage 1-5 CKD and 50.8% of patients with stage 1-4 CKD had PHT. Additionally, the prevalence of PHT in the stage 1-4 CKD patients and stage 5 patients was similar. Studies on
non-dialysis-dependent stage 5 CKD patients reported that the prevalence of PHT ranges from 9-39% and that the prevalence of PHT is higher in patients undergoing dialysis than in non-dialysis patients (9-12). In the present study the prevalence of PHT in patients with stage 5 CKD not undergoing HD was 58.3%, which is higher than reported earlier (9,11,13,14). In addition, there weren’t any significant differences in sPAP or the prevalence of PHT between the patients undergoing and not undergoing HD.

The prevalence of PHT in the present study’s stage 1-4 patients was 50.8% - the most noteworthy of the present study’s findings. Accordingly, we think in addition to CKD patients undergoing HD early-stage CKD patients should also be considered high risk patients. In most studies on patients with CKD, sPAP has been estimated as Doppler-derived sPAP and various sPAP cut-offs have been used, ranging from 25 to ≥45 mmHg (9,11,13-15). In the present study sPAP ≥35 mmHg based on Doppler echocardiography was considered diagnostic for PHT and the high prevalence of PHT in this study may be explained due to the lack of uniformity in diagnostic criteria and sPAP cutoffs in the literature. Right-sided cardiac catheterization is the gold standard for the diagnosis of PHT, but Doppler echocardiography measurement of sPAP was also correlated with measurement obtained via catheterization, without the risks associated with an invasive test procedure (15). The present study and most other studies on CKD and PHT used Doppler echocardiography-derived PAP measurements.

Frucher et al. studied 191 CKD patients and reported that HD was the third most common cause of PHT, accounting for 13% of cases of PHT (16). Uremia (leading to pulmonary arterial vasoconstriction), the presence of an AVF, low bioavailability of nitric oxide (17), an elevated endothelin level (18,19), vascular calcification, hypervolemia, exposure to dialysis membranes, endothelial dysfunction, and anemia (20,21) are the reported pathogenetic mechanisms for the development of PHT in patients with CKD. Patients with an AVF had a high incidence of PHT due to increased cardiac output and it has been reported that the incidence of PHT in stage 5 CKD patients with an AVF was 40-50% (12,22). Although Havlucu et al. (11) showed that the presence of PHT in patients with an AVF was significantly higher than that in patients without an AVF, Yigla et al. (9) reported that mean sPAP significantly decreased after successful renal transplantation in CKD patients, while their AVF was intact. It was reported that compression of AVF can decrease cardiac output and sPAP, and that an AVF increases sPAP via elevation of cardiac output (23). In the present study the prevalence of PHT in stage 5 CKD patients with and without an AVF was similar (53.3% vs. 58.3%, respectively) and, as previously reported, there wasn’t an association between the presence of an AVF and PHT (24,25). Anemia can also contribute to the development of PHT by increasing cardiac output and exacerbating hypoxia (26). In the present study there wasn’t a significant difference in the hemoglobin level between the patients with and without PHT, as reported earlier (27,28).

Vascular calcification is a common and important risk factor for cardiovascular death in patients with CKD. Impaired Calcium-phosphorus balance and secondary hypoparathyroidism play an important role in the pathogenesis of vascular calcification (29). Although researches has shown that there isn’t an association between pulmonary calcification and the PTH level (30,31), it was also reported that in dogs with experimentally induced CKD

| Table 1: Clinical and laboratory characteristics of the study groups |
|-----------------|-----------------|
| Variables       | Mean ± SD       |
| Age (year)      | 55.4±15.2       |
| Sex             |                 |
| Male (n, %)     | 94 (54.7)       |
| Female (n, %)   | 78 (45.3)       |
| Stage (n, %)    |                 |
| 1-2             | 36 (21)         |
| 3               | 44 (25)         |
| 4               | 38 (22)         |
| 5               | 54 (32)         |
| Etiology (n, %) |                 |
| HT              | 42 (25)         |
| DM              | 34 (20)         |
| PKD             | 28 (16)         |
| Transplant      | 12 (7)          |
| Glomerulonephritis | 12 (7)      |
| TIN             | 20 (12)         |
| Unknown         | 24 (14)         |
| Laboratory variables |       |
| Urea (mg/dL)    | 88.2±49         |
| Creatinine (mg/dL) | 3.5±3.1    |
| Na              | 137.9±3.6       |
| K               | 4.6±0.7         |
| Ca (mg/dL)      | 9±0.9           |
| P (mg/dL)       | 4±1.1           |
| PTH (pg/mL)     | 191.5±230.1     |
| Hemoglobin (g/dL) | 12.5±2.8     |
| sPAP (mmHg)     | 34.5±5.7        |

HT: Hypertension, DM: Diabetes mellitus, PKD: Polycystic kidney disease, TIN: Tubulointerstitial nephritis, PTH: Parathyroid hormone, sPAP: Systolic pulmonary arterial pressure, Ca: Calcium, SD: Standard deviation
an elevated PTH level might induce right ventricular pressure, right ventricular hypertrophy, and pulmonary resistance without pulmonary calcification (32). Secondary hyperparathyroidism and an elevated PTH level in a uremic environment have been implicated in many cases of vascular calcification. The present study did not evaluate pulmonary calcification formation, but in this study, as in Havlucu et al. (11) and Kumbar et al. (33), the serum PTH level was significantly higher and the serum Ca level was significantly lower in the patients with PHT (p<0.05); however, Amin et al. (30) and Unal et al. (25,27) reported that there wasn’t a significant difference in PTH between CKD patients with and without PHT. They also reported that there wasn’t a correlation between the Ca level and PHT.

Endothelial dysfunction, a common finding in CKD patients, and such comorbid conditions as hypertension, diabetes mellitus, and diastolic dysfunction have also been suggested to contribute to PHT (31). Although the prevalence of hypertension was significantly lower in the present study’s CKD patients with PHT than in those without PHT, blood pressure was similar and there were no diastolic dysfunction on echocardiographic measurement between patients with PHT and without PHT. Although hypertension and diabetes mellitus were the most common primary diseases in the present study, there wasn’t an association between the prevalence of PHT and primary renal disease. The present findings support the notion that hormonal-metabolic factors play a role in the development of PHT. The prevalence of PHT was similar in the stage 1-4 CKD patients and stage 5 patients, there wasn’t an association between PHT, and an AVF or HD, and the PHT level in the CKD patients with PHT was higher than in those without PHT.

The present study has several limitations. The sample was small and sPAP was noninvasively measured via Doppler echocardiography. Unfortunately, the mechanisms of PHT were not investigated. To the best of out knowledge the present study

### Table 2: sPAP and prevalence of parathyroid hormone in each stages of chronic kidney disease

| Stages       | sPAP (mmHg) | PHT (n, %) | p  |
|--------------|-------------|------------|----|
| 1            | 34.8±5.8    | 16 (57.1)  | 0.32|
| 2            | 28.3±2.5    | 14 (50.8)  |    |
| 3            | 34.5±4.7    | 24 (54.5)  |    |
| 4            | 34.7±7.5    | 20 (52.6)  |    |
| 5            | 35.2±4.8    | 30 (55.6)  |    |
| Stage 1-4    | 34.2±6.0    | 60 (50.8)  | 0.86|
| Stage 5      | 35.2±4.8    | 30 (55.6)  |    |
| Stage 5 with AVF | 34.5±5.3 | 16 (53.3)  | 0.47|
| Stage 5 without AVF | 36±6.3   | 14 (58.3)  |    |

AVF: Arteriovenous fistula, sPAP: Systolic pulmonary arterial pressure, PHT: Pulmonary hypertension

### Table 3: Comparison of parameters in patients with and without pulmonary hypertension

|                     | Patients without PHT (n=82) | Patients with PHT (n=90) | p  |
|---------------------|-----------------------------|--------------------------|----|
| Age (year)          | 55.2±15.1                   | 55.6±15.5                | 0.91|
| Gender (n)          |                             |                          |    |
| Male                | 38                          | 56                       | 0.20|
| Female              | 44                          | 34                       |    |
| Systolic blood pressure (mmHg) | 131.2±21.5     | 128.0±29.8               | 0.570|
| Diastolic blood pressure (mmHg) | 76.8±14.4   | 76.9±14.6                | 0.985|
| LVEDD (cm)          | 4.2±0.4                     | 4.3±0.3                  | 0.34|
| Ca (mg/dL)          | 9.3±0.6                     | 8.8±1                    | 0.026|
| p (mg/dL)           | 3.8±1                       | 4.1±1.2                  | 0.289|
| Hb (g/dL)           | 12.4±1.8                    | 12.5±3.5                 | 0.795|
| PTH (pg/mL)         | 79.6 (5.4-1420)             | 133.5 (9.6-697)          | 0.032|
| HT (n, %)           | 60 (73.2)                   | 44 (48.9)                | 0.038|

LVEDD: Left ventricular end-diastolic diameter, Hb: Hemoglobin, PHT: Pulmonary hypertension, HT: Hypertension, Ca: Calcium
is the first to assess the prevalence of PHT in early stages of CKD patients and, based on the present findings, we think additional larger scale studies are needed to more clearly understand the long-term effects of PHT in CKD patients.

**Conclusion**

As the presence of PHT is prognostically important in patients with end-stage renal disease, the present study investigated PHT in early-stage CKD patients. The present findings show that the prevalence of PHT in all stages of CKD was high. Renal disease itself, rather than an AVF, appeared to be the primary risk factor for PHT. Due to the high morbidity and mortality rates associated with PHT, systematic screening using Doppler echocardiography might be indicated in all CKD patients for early recognition.

**Conflict of Interest Statement**

The authors declare there are no conflicts of interest-financial or otherwise-related to the materials presented herein.

**Authorship Contributions**

Idea/Hypothesis: Ezgi Coskun Yenigun, Design: Ezgi Coskun Yenigun, Sevket Balli, Data Collection: Sukran Gurses, Data Analysis/Interpretation: Ramazan Ozturk, Ezgi Coskun Yenigun, Literature Review: Didem Turgut, Critical Review: Eyup Koc, Fatih Dede

**References**

1. Martin KB, Klinger JR, Rounds SI. Pulmonary arterial hypertension: New insights and new hope. Respirology. 2006;11:6-17.

2. Yigla M, Dabbah S, Azzam ZS, Rubin ZS, Reisner SA. Background diseases in 671 patients with moderate to severe pulmonary hypertension. Isr Med Assoc J. 2000;2:684-689.

3. Galië N, Hoepner MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30:2493-2537.

4. Bolignano D, Rastelli S, Agarwal R, Fliser D, Massy Z, Ortiz A, et al. Pulmonary Hypertension in CKD. Am J Kidney Dis. 2013;61:612-622.

5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and Management of chronic kidney disease. Kidney Inter. 2013;3:1-150.

6. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007;53:766-772.

7. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J Am Coll Cardiol. 1985;6:359-365.

8. Rosenkranz S. Pulmonary hypertension: Current diagnosis and treatment. Clin Res Cardiol. 2007;96:527-541.

9. Yigla M, Nakhoul F, Sabag A, Tov N, Gorevich B, Abassi Z, et al. Pulmonary hypertension in patients with end-stage renal disease. Chest. 2003;123:1577-1588.

10. Tarrass F, Benjelloun M, Medkouri G, Hachim K, Berghenam MG, Ramdani B. Doppler echocardiography evaluation of pulmonary hypertension in patients undergoing hemodialysis. Hemodial Int. 2006;10:356-359.

11. Havlucu Y, Kursat S, Ekmekci C, Celik P, Serter S, Bayturun O, et al. Pulmonary hypertension in patients with chronic renal failure. Respiration. 2007;74:503-510.

12. Nakhoul F, Yigla M, Gilman R, Reisner SA, Abassi Z. The pathogenesis of pulmonary hypertension in haemodialysis patients via arteriovenous access. Nephrol Dial Transplant. 2005;20:1686-1692.

13. Yigla M, Fruchter O, Aharonson D, Yanay N, Reisner SA, Lewin M, et al. Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients. Kidney Int. 2009;75:969-975.

14. Issa N, Krowka MJ, Griffin MD, Hickson LJ, Stegall MD, Cosio FG. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. Transplantation. 2008;86:1384-1388.

15. Badesch DB, Champion HC, Sanchez MA, Hoepfer MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;54(Suppl 1):55-66.

16. Fruchter O, Yigla M. Underlying aetiology of pulmonary hypertension in 191 patients: A single centre experience. Respirology. 2008;13:825-831.

17. Arese M, Strasly M, Ruva C, Costamagna C, Ghigo D, MacAllister R, et al. Regulation of nitric oxide synthesis in uremia. Nephrol Dial Transplant. 1995;10:1386-1397.

18. Stefanidis I, Wurth P, Mertens PR, Ikonomov V, Philippidis G, Golphinopoulos S, et al. Plasma endothelin-1 in hemodialysis treatment: the influence of hypertension. J Cardiovasc Pharmacol. 2004;44(Suppl 1):43-48.

19. Odetti P, Monacelli F, Storace D, Robaudo C, Rossi S, Deferrari G, et al. Correlation between pentosidine and endothelin-1 in subjects undergoing chronic hemodialysis. Horm Metab Res. 2006;38:817-820.

20. Buemi M, Senatore M, Gallo GC, Crascì E, Campo S, Sturiale A, et al. Pulmonary hypertension and erythropoietin. Kidney Blood Press Res. 2007;30:248-252.
21. Milliner DS, Zinsmeister AR, Lieberman E, Landing B. Soft tissue calcification in pediatric patients with end-stage renal disease. Kidney Int. 1990;38:931-936.

22. Ifudu O. Care of patients undergoing hemodialysis. N Engl J Med. 1998;339:1054-1062.

23. Yigla M, Abassi Z, Reisner SA, Nakhoul F. Pulmonary hypertension in hemodialysis patients: An unrecognized threat. Semin Dial. 2006;19:353-357.

24. Pabst S, Hammerstingl C, Hundt F, Gerhardt T, Grohé C, Nickenig G, et al. Pulmonary hypertension in patients with chronic kidney disease on dialysis and without dialysis: Results of the PEPPER-study. PLoS One. 2012;7:35310.

25. Unal A, Tasdemir K, Oymak S, Duran M, Kocyigit I, Oguz F, et al. The long-term effects of arteriovenous fistula creation on the development of pulmonary hypertension in hemodialysis patients. Hemodial Int. 2010;14:398-402.

26. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med. 2009;179:615-621.

27. Unal A, Sipahioglu M, Oguz F, Kaya M, Kucuk H, Tokgoz B, et al. Pulmonary hypertension in peritoneal dialysis patients: Prevalence and risk factors. Perit Dial Int. 2009;29:191-198.

28. Bozbas SS, Akcay S, Altin C, Bozbas H, Karacaglar E, Kanyilmaz, et al. Pulmonary hypertension in patients with end-stage renal disease undergoing renal transplantation. Transplant Proc 2009;41:2753-2756.

29. Davies MR, Hruska KA. Pathophysiological mechanisms of vascular calcification in end-stage renal disease. Kidney Int. 2001;60:472-479.

30. Amin M, Fawzy A, Hamid MA, Elhendy A. Pulmonary hypertension in patients with chronic renal failure: Role of parathyroid hormone and pulmonary artery calcifications. Chest. 2003;124:2093-2097.

31. Yigla M, Keidar Z, Safadi I, Tov N, Reisner SA, Nakhoul F. Pulmonary calcification in hemodialysis patients: Correlation with pulmonary artery pressure values. Kidney Int. 2004;66:806-810.

32. Akmal M, Barndt RR, Ansari AN, Mohler JG, Massry SG. Excess PTH in CRF induces pulmonary calcification, pulmonary hypertension and right ventricular hypertrophy. Kidney Int. 1995;47:158-163.

33. Kumbar L, Fein PA, Rafiq MA, Borawski C, Chattopadhyay J, Avram MM. Pulmonary hypertension in peritoneal dialysis patients. Adv Perit Dial. 2007;23:127-131.