



Evaluation of pulmonary hypertension and its relationship with serum parathyroid hormone levels in hemodialysis patients

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ABSTRACT

Introduction: Pulmonary hypertension is a progressive and severe disease associated with left or right ventricular dysfunction and is common in patients under hemodialysis. One of the factors in its development is parathormone but this relationship is unclear.

Objectives: In this study, the difference between serum levels of parathyroid hormone (PTH) in hemodialysis patients with and without pulmonary artery hypertension (PAH) was investigated.

Patients and Methods: We conducted a cross-sectional study among hemodialysis patients referred to a tertiary hospital in Iran. Characteristics of coronary artery and pulmonary arteries were recorded by echocardiography. The laboratory data were measured and recorded. Statistical analysis was performed at 95% confidence level and with a significance level of less than 5%.

Results: Of 65 enrolled patients, 41 had normal pulmonary artery pressure, and 24 had pulmonary hypertension. The mean age in patients with and without pulmonary hypertension was significantly different ($P=0.010$). There was no significant difference in serum PTH levels between patients with and without pulmonary hypertension ($P=0.496$). The mean serum levels of calcium, albumin, triglyceride, and cholesterol in two groups of patients with and without pulmonary hypertension was not significantly different ($P=0.906$).

Conclusion: In our study, no significant correlation between pulmonary hypertension and PTH was detected. The prevalence of pulmonary arterial hypertension in our study was relatively high, suggesting the need to pay attention to pulmonary hypertension in hemodialysis patients

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

Pulmonary hypertension is common in patients under hemodialysis. One of the factors in its development is parathormone, however, this relationship is unclear. We assessed the relationship between serum levels of PTH in hemodialysis patients with and without pulmonary artery hypertension, though our study showed no significant correlation between pulmonary hypertension and PTH. The prevalence of PAH in our study was relatively high, suggesting the need to pay attention to pulmonary hypertension in hemodialysis patients.

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Introduction

Chronic renal failure encompasses a range of different pathophysiological processes associated with abnormal renal function and a progressive decrease in glomerular filtration rate (GFR) (1). End-stage renal disease (ESRD) is the fifth stage of chronic renal failure. At this stage, GFR is reduced to less than 15 cc/min, and the accumulation of toxins, fluid, and electrolytes excreted by the kidneys leads to the uremic syndrome. This syndrome can lead to death if left untreated with alternative kidney therapy, including dialysis or kidney transplant (1). The incidence of ESRD is 357 cases per million people annually, with an increasing incidence worldwide (2). Complications include anemia, electrolyte abnormalities, disturbances in bone metabolism, metabolic acidosis, increased risk of cardiovascular and chronic lung diseases, increased risk of infections, and neurological disorders (1).

Cardiovascular disease (CVD) is the leading cause of mortality and disability in ESRD patients (3). Left ventricular hypertrophy, myocardial interstitial fibrosis, increased arterial wall thickness, coronary artery calcification are the main symptoms of CVD (4). The high mortality rate from CVD in ESRD patients has been reported in clinical and epidemiological studies (5). Although risk factors such as diabetes mellitus, hypertension, dyslipidemia, and old age are common in ESRD patients, there are other reasons for the high prevalence of CVD in these patients (6). Pulmonary hypertension is a cardiac complication among ESRD patients, a progressive and fatal disease caused by pulmonary circulation and associated with left or right ventricular failure (7).

An increase in PAP exceeding 35 mm Hg is measured by echocardiography (8). This condition occurs when the pulmonary arteries become obstructed or narrowed, thereby in response to this increase in pressure, especially the right ventricle, cardiac muscles should act more strongly to pump blood into the pulmonary artery; since continuing this condition exacerbates heart failure over time (9).

Although the prevalence of pulmonary hypertension has been reported differently in various studies, the prevalence of pulmonary hypertension in hemodialysis patients has been reported in recent researches to be between 17% and 56% (10). Its prevalence is estimated to be approximately 17% to 40% in transplant prone patients (11). Since, there are several strong explanations for development and progression of pulmonary arterial hypertension in patients undergoing continuous hemodialysis, the pathogenesis of pulmonary hypertension in hemodialysis patients is still unknown (10). ESRD-related hormonal and metabolic dysfunction increases pulmonary artery vasoconstriction and, as a result, pulmonary vascular resistance, which is effective in causing pulmonary hypertension (12).

Some studies have reported a significant relationship

between reduced serum albumin, triglyceride, cholesterol, body mass index (BMI) as criteria for nutritional status and increased prevalence of pulmonary hypertension in hemodialysis patients. However, studies have been few, and the results have been different (10).

Another possible reason for increased pulmonary vascular resistance is vascular calcification, which is common in ESRD patients (11). Vascular calcification is a common type of extra-bone calcification in ESRD, which is now identifiable by non-invasive techniques (13). Available evidence suggests that abnormal parathyroid hormone (PTH) levels cause vascular calcification, which increases the risk of cardiovascular mortality and morbidity in ESRD patients (14). Increased PTH-induced by secondary hyperparathyroidism occurs in ESRD and hemodialysis patients due to the effect of hyperphosphatemia and hypocalcemia on parathyroid gland receptors (14). CVD in dialysis patients can be exacerbated in the context of vascular calcification and ventricular dysfunction due to pulmonary hypertension (15). PTH causes calcium entry into many cells, while high PTH levels in the blood are associated with increased calcium entry into various tissues (14). An increase in the prevalence of pulmonary hypertension and the relationship of pulmonary hypertension-hyperparathyroidism in pre-dialysis patients with chronic kidney disease and hemodialysis patients with chronic renal disease has been reported (8).

A previous study showed a positive and significant correlation was found between pulmonary artery systolic pressure (PASP) and iPTH (intact PTH) in hemodialysis patients (14). Experimental studies have shown the relationship between hyperparathyroidism and pulmonary artery calcification and pulmonary hypertension in animal models of chronic renal failure. Meanwhile, an increase in the prevalence of pulmonary hypertension and its association with hyperparathyroidism has been reported in patients with chronic renal disease and patients undergoing hemodialysis (10).

In a study by Genctoy et al, pulmonary arterial hypertension in patients with chronic renal disease revealed pulmonary artery hypertension in 35.9% of patients. Meantime, patients with pulmonary arterial hypertension had higher PTH levels (10). The effect of serum PTH concentration on pulmonary arterial hypertension is due to increased calcium content in vascular smooth muscle cells (16). Pulmonary hypertension can have adverse effects on the quality of life of hemodialysis and ESRD patients (17).

Recent studies have been conducted on the prevalence of pulmonary hypertension and its association with PTH in hemodialysis patients whose results have been controversial (8,18). Given that early awareness of pulmonary hypertension before pathophysiological changes may help to prevent it, knowing its associated

factors, such as screening, early diagnosis and treatment of pulmonary hypertension, reduce its effects and improve the course of the disease. Early intervention can also prevent exacerbation of heart failure and mortality from pulmonary hypertension (19).

Objectives

Evaluation of prevalence of pulmonary hypertension in hemodialysis patients and its relationship with serum PTH level for timely therapeutic interventions can play an essential role in improving the quality of life of hemodialysis patients, improving disease status, reducing costs, increasing patient survival and reducing mortality and disability. In this study, the relationship between serum levels of PTH in hemodialysis patients with and without pulmonary artery hypertension was investigated.

Patients and Methods

Study design

A cross-sectional descriptive-analytical study was conducted in hemodialysis patients referred to Kosar medical center, Semnan, Iran in 2016 and 2017 were included.

Inclusion criteria were hemodialysis patients over 18 years old who underwent hemodialysis through fistula or graft for at least three months and underwent hemodialysis three times a week for 3 to 4 hours each. All hemodialysis patients under the age of 18 and patients with cancer, active heart or lung disease, active infection and vascular collagen diseases were excluded.

Demographic information checklist and paraclinical and clinical findings were used for data collection. Patients underwent echocardiography (Affiniti 50C, Phillips, Netherland) for traditional echocardiographic approach to estimate PASP (20), and PAP indices. Normal PAP at rest is $14+3$ mm Hg with an upper limit of normal of approximately 20 mm Hg (21). Echocardiography is a highly accurate non-invasive method for measuring pulmonary arterial blood pressure and its correlation coefficient with catheterism method was $r = 0.97$. Based on their pulmonary hypertension, these patients were divided into two groups with and without pulmonary hypertension. Serum levels of calcium, phosphorus, PTH, albumin, fasting blood glucose, total cholesterol, triglyceride and hemoglobin were measured simultaneously with dialysis. Patients with hypertension were compared with patients with normal pulmonary blood pressure in terms of serum parathyroid levels.

Ethical considerations

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients. The Ethics Committee of Semnan University of Medical Sciences approved this study (ethical code #IR.SEMUMS.REC.1394.131). The source of data used in this

paper was from the MD thesis of Soheila Jafari, at School of Medicine, Semnan University of Medical Sciences, Semnan, Iran (Grant # 928).

Statistical analysis

Data were analyzed using *t* test or its nonparametric equivalent (Mann-Whitney U test) for quantitative variables and chi-square or Fisher's exact test for qualitative variables. Numerical variables were reported as arithmetic mean \pm SD. In all tests, the confidence level was 95%, and the significance level was less than 5%. Data analysis was performed using SPSS version 21.

Results

In this study, 65 patients undergoing hemodialysis were evaluated for pulmonary hypertension. Around 32 patients were male (49.2%), and 33 were female (50.8%). Of 65 hemodialysis patients, 41 (63%) had normal pulmonary blood pressure, and 24 (37%) had high pulmonary hypertension. The frequency of pulmonary hypertension was not significantly different between the genders ($P=0.619$).

The mean (\pm SD) age of the patients was 63.06 ± 14.2 years. The mean age of patients with and without pulmonary hypertension was 69.33 ± 11.8 and 59.39 ± 15.9 years, respectively, which was significantly different ($P=0.010$, independent *t* test).

The mean duration of dialysis in patients with pulmonary hypertension was 4.21 ± 3.6 years and 3.20 ± 3.1 years in patients without pulmonary arterial hypertension, with no significant difference ($P=0.223$).

Mean (\pm standard deviation) of laboratory parameters including plasma hemoglobin, serum albumin, calcium, triglyceride, cholesterol, and parathormone were compared in patients with and without pulmonary hypertension. Apart from the mean of hemoglobin level, the other parameters were not significantly different between the two groups (Table 1).

The mean serum PTH level was not significantly different between the two genders in patients with pulmonary hypertension (Table 2). Mean of serum PTH levels were also compared between male and female patients with normal pulmonary blood pressure, indicating no significant difference in this group ($P=0.911$).

There was no significant relationship between serum PTH level and mean age in patients with pulmonary hypertension ($r=-0.030$, $P=0.891$). There was no significant relationship between serum PTH level in patients with normal pulmonary blood pressure and age too ($r = -0.268$, $P=0.090$).

By dividing patients into four age groups (younger than 45, 45-60, 61-75 years and older than 75 years), mean PTH levels were compared between these four age groups in patients with normal blood pressure and high pulmonary hypertension. No significant difference was found

Table 1. Laboratory parameters in enrolled patients and a comparison between patients with and without pulmonary hypertension

Parameter	Hemodialysis patient with pulmonary hypertension (Mean±SD)	Hemodialysis patient without pulmonary hypertension (Mean±SD)	P value
Albumin (g/dL)	0.5 ±3.73	3.74 ± 0.4	0.914
Cholesterol (mg/dL)	137.54 ± 19.8	130.63 ± 29.5	0.313
Triglyceride (mg/dL)	124.23 ± 39.0	115.15 ± 44.6	0.406
Calcium (mg/dL)	8.82 ± 0.7	8.80 ± 0.8	0.906
Hemoglobin (g/dL)	11.29 ± 1.0	10.54 ± 1.4	0.031
Parathormon (pg/mL)	72.69 ± 117.7	112.69 ± 270.7	0.496

Table 2. Comparison of iPTH levels between patients with and without pulmonary hypertension in both genders

Gender	Pulmonary hypertension	iPTH (pg/mL) (Mean ± SD)	95% CI		P value
			Upper	Lower	
Male	Normal	118.12 ± 294.02	225.04	-113.34	0.505
	High	62.27 ± 108.08	211.34	-99.64	
Female	Normal	108.43 ± 257.66	197.98	-155.62	0.809
	High	87.26 ± 134.62	161.25	-118.87	

iPTH, intact parathyroid hormone.

(Kruskal Wallis test, $P=0.227$ and $P=0.557$ respectively).

Discussion

The main finding of this study was the insignificant association between gender, duration of hemodialysis, parathormone level, and other laboratory parameters except for hemoglobin level with elevated pulmonary artery pressure (PAP). There was no significant difference regarding the mean age of participants in the cases with or without pulmonary artery hypertension (PAH). Meanwhile, The prevalence of pulmonary arterial hypertension in our study was relatively high.

The prevalence of pulmonary hypertension and its association with laboratory parameters, parathormone and other parameters have been evaluated and its relationship with PTH in hemodialysis patients has been controversial (8,18).

Mukhtar et al reported the prevalence of pulmonary hypertension in hemodialysis patients was 56%. The prevalence of pulmonary hypertension was also significantly correlated with gender and was more prevalent in women (22). Our study yielded opposite results. In our study, the prevalence of PAH was higher in females but was not significantly different from males. The duration of dialysis was higher in patients with pulmonary hypertension compared to those with the normal pulmonary arterial blood pressure, however the difference was not significant.

Li et al in China reported a prevalence of pulmonary hypertension measured by echocardiography was 18.1%. The study noted that PAH was associated with a higher risk of developing heart failure and this risk increased as pulmonary hypertension increased (23). In our study, the

prevalence of pulmonary hypertension was 37%, much higher than the Li and colleagues' study, and significantly lower than that of the study by Mukhtar et al (22). Bolognani et al reported a prevalence of PAH of 23% (24). In this study, pulmonary arterial hypertension has been shown to increase CVD and mortality. The prevalence of pulmonary hypertension in this study is higher than that of Li et al (23). These differences may be attributed to differences in centers, instruments of measurement, and geographical differences.

Emara et al reported the prevalence of pulmonary hypertension in hemodialysis patients at 41.5%. In their study, hemoglobin levels in patients with high pulmonary hypertension were lower than those without pulmonary hypertension. Moreover, PTH levels were significantly higher in patients with pulmonary hypertension than in patients with normal pulmonary blood pressure (18). The finding in our study indicated that hemoglobin levels in patients with pulmonary hypertension were significantly higher than those in subjects with normal pulmonary arterial blood pressure which is inconsistent with the study conducted by Emara et al (18).

The results of Zhang et al regarding hemoglobin level (25) are in contrast to our study that blood hemoglobin level was significantly higher in people with pulmonary hypertension than in those with normal pulmonary blood pressure. In our study, there was no significant relationship between parathormone level, duration of dialysis, gender and laboratory parameters in two groups of patients with and without pulmonary hypertension, which is inconsistent with the study by Zhang et al. Perhaps this contradiction can be attributed to the fact that Zhang et al studied CKD patients of stage one to fifth since our study

only examined dialysis patients, while the treatments received in these patients are effective on the difference in hemoglobin level in two groups of patients with and without pulmonary hypertension.

In their study, Rostand and Drüeke, studying the effect of PTH and vitamin D on the cardiovascular system, reviewed articles on the topic of PTH, vitamin D and its association with CVD in patients with chronic renal failure (CRF). The results of this review study indicate that PTH and vitamin D in uremic patients is associated with cardiovascular pathological changes and even increase cardiovascular mortality (26). Our study only compared parathormone and calcium levels and other laboratory parameters in patients with chronic renal failure with normal and elevated pulmonary arterial blood pressure, with no difference in the levels of the parameters mentioned between patients with and without pulmonary blood pressure. Perhaps the reason for the inconsistency of our results with Rostand and Drüeke's results is that they included patients with CRF in their study, while our study included only patients undergoing hemodialysis. Another finding of our research is that hemoglobin levels are higher in patients with pulmonary arterial hypertension than in patients with normal pulmonary blood pressure. The feedback effect of long-term hypoxia can explain this in patients with PAH on the number of red blood cells. Moreover, the association between elevated hemoglobin and pulmonary hypertension is necessary to treat hemodialysis anemia patients to maintain hemoglobin levels between 11 and 12 g/dL according to the National Kidney Disease Outcomes Quality Initiative (KDOQI) Foundation guideline and no more than this (27).

Amin et al examined the relationship between pulmonary hypertension and pulmonary artery calcification and hyperparathyroidism in CRF patients undergoing hemodialysis. They found 15 (29%) patients had pulmonary hypertension and proportion of women was slightly higher. In their study, the parameters of age, calcium, alkaline phosphatase, duration of dialysis, phosphorus and parathormone level were not significantly different in patients with chronic renal failure with and without pulmonary hypertension (28). Our study had similar results to their study. Our study also investigated the relationship between pulmonary hypertension and hyperparathyroidism in patients undergoing hemodialysis. In our study, the prevalence of hypertension among hemodialysis patients was 37%, and the proportion of women was slightly higher. However, the prevalence of pulmonary hypertension was not significantly different between the two genders. In our study, the parameters of serum calcium, dialysis duration and parathormone level were not significantly different between patients with and without pulmonary hypertension. In our study, other parameters, including cholesterol, triglyceride and hemoglobin, were also compared between the two groups

of patients with and without pulmonary hypertension. The only difference in hemoglobin was significant in these two groups, and the mean of hemoglobin was higher in patients with pulmonary hypertension.

In the study of Kim et al, the relationship between PTH and pulmonary arterial blood pressure in patients undergoing maintenance hemodialysis therapy was examined. PTH and PAP (echocardiography) were measured in all patients. About 36.6% of hemodialysis patients had pulmonary hypertension. In this study, dialysis duration (months) had no significant difference between patients with and without pulmonary hypertension and there was not a significant relationship between PASP and PTH levels (29). The studied population in the study by Kim et al and our study were hemodialysis patients. In our study, the prevalence of pulmonary hypertension was 36.9% which is similar to the study conducted by Kim et al (36.6%). In our study, no significant relationship between the level of parathormone, dialysis duration, gender and laboratory parameters in two groups of patients with and without pulmonary hypertension was seen. However, in our study, mean age and hemoglobin levels in patients with and without pulmonary hypertension were significantly different. Despite to similarity of target population in Kim and colleagues' study and our study, however, there are a few inconsistency in results. These inconsistencies are due to sample size, the treatments that patients received in two separate centres, and breakdown of patients based on causes of pulmonary hypertension.

Conclusion

In our study, the prevalence of PAH was relatively high; due to its cardiovascular complications suggesting the need to pay particular attention to PAH in hemodialysis patients. No significant association was observed between PAH and PTH. However, the level of hemoglobin was higher in patients with pulmonary hypertension compared to those without it and emphasized the avoidance of anemia over-treatment in dialysis patients.

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Authors' contribution

RE, SJ, ZAS, MB, RA and SMSI provided technical assistance, collection and preparation of the manuscript. MM acted as a biostatistics consultant. RE and MY designed, supervised the study and prepared the final draft of the article.

Limitations of the study

The most important limitation of this study was the lack of a control group to compare the prevalence of pulmonary hypertension and its relationship with serum PTH levels in hemodialysis patients with control group.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

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

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