ORIGINAL ARTICLE

The Prevalence and Correlates of Pulmonary Hypertension in End Stage Renal Disease

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Abstract

Objective; To evaluate the incidence of unexplained pulmonary hypertension (PH) in end- stage renal disease (ESRD) and to evaluate its possible relationship with some clinical and biochemical parameters.
Patients and Methods; This study was conducted retrospectively at Prince Rashed Hospital (PRH), North of Jordan, on patients undergoing maintenance hemodialysis (HD) during August 2009 to August 2010.Demographic and clinical data were obtained from charts review and Patients themselves. 2Dimensional echocardiography (2DECHO) was performed in all patients. Blood samples were taken for parathormone (PTH) and other biochemical measurements. SPSS package was used for statistical analysis.Statistical significance was considered at p value < 0.05.
Results; A total of 131 hemodialysis (HD) patients were included in the study, of them 76 (58, 9%) were men. The mean age of the study population was 53.7 + 16.2 yrs. Pulmonary hypertension (pulmonary artery pressure (PAP)=47+3, range 35-79mmHg) was detected in 52 patients (39.6%).The levels of PAP were positively correlated with serum intact parathormone (iPTH) levels, age, duration of HD, mean arterial pressure (MAP), interventricular septal (IVS) thickness, cardiac output(CO), and serum levels of phosphorus , creatinine, whereas the levels of PAP were inversely correlated with the levels of serum calcium and hemoglobin(Hb).
Conclusion; Pulmonary hypertension is a frequent finding in end stage renal disease and mineral disorders together with secondary hyperparathyroidism (SHPTH), increased cardiac output and anemia may be involved in the pathogenesis of this abnormality. The early detection and treatment of pulmonary hypertension aiming to decrease its serious complications is mandatory.

Key words; Pulmonary hypertension, mineral metabolism, echocardiography, end- stage renal disease. Prince Rashed Hospital.

Introduction

The pulmonary artery pressure at the sea level normally ranges between 18-25 mmHg. Systolic and mean PAPs above 30 and 20 mmHg respectively are diagnostic of pulmonary hypertension (1). According to a recent classification, PH can be classified into five types; arterial, venous, hypoxic, thromboembolic, or miscellaneous (2).Pulmonary hypertension is increasingly recognized as factor that can affect the mortality and morbidity in chronic renal disease (CRD). Nevertheless in many patients without renal disease, PH has also been associated with worse outcome and most cases of PH are consequent to myocardial or pulmonary disease (3, 4). However, in the setting of CRD, PH is a very frequent finding (5).This may be explained by the increased prevalence of co-morbidities potentially leading to PH, such as left ventricular failure, chronic obstructive pulmonary diseases, chronic anemia, sleep apnea, collagen vascular diseases, HIV infection and portal hypertension. Additionally the majority of ESRD patients have an arteriovenous fistula that results in AV shunting and potentially PH. In addition SHPTH, elevated Ca x P product, and vascular calcifications are commonly seen in CRD (6,7).Furthermore in animal models and human studies it has been shown that excess parathyroid hormone in CKD leads to pulmonary calcification, PH, and right ventricular failure (8,9).Other studies demonstrated that many HD patients develop decreased nitric oxide (NO) levels leading to endothelial dysfunction that reduces the capacity of the pulmonary circulation, resulting in failure to maintain the elevated CO due to the A-V access, leading to the development of PH.(10) The diagnosis of PH at the recent years can be accurately performed by Doppler echocardiography which enabled the

noninvasive techniques in the diagnosis of many cardiovascular diseases (11). A number of drugs have been introduced for the treatment of primary and secondary PH. In this regard a relatively small number of trials supported the use of these agents and many have no data on mortality benefit or the natural history of the disease. (12).However, the early intervention to reduce PAP in CRD may improve the cardiac status and decrease mortality. This may be achieved by a number of therapeutic modalities including effective hemodialysis together with prevention and treatment of SHPTH (8, 9).The aim of this study was to evaluate the prevalence and correlates of unexplained PH in HD patients, and to try to suggest some resolutions potentially able to decrease the morbidity and mortality of this disease.

Methods and materials

This is a retrospective study which was performed in patients undergoing chronic HD at PRH during August 2009 to August 2010.Patients with co-morbidities potentially able to cause PH were excluded from the study. Demographic and clinical data regarding age, duration on HD, drug history, history of DM, HTN, and smoking, were obtained from charts review and patients themselves. All our study patients were on treatment For SHPTH with oral vitamin D3 sterols and calcium carbonate, both prescribed in different doses. Hemodialysis protocol at PRH was 3-4 hours, twice to thrice weekly. Blood pressure readings were taken three times consecutively after 10 minutes of rest, at 2- minute intervals with one automatic blood pressure monitor, taking the mean of the three readings. MAP was calculated using the formula: MAP = 2/3 diastolic pressure + 1/3systolic pressure.as mean + Peripheral Venous blood samples were taken for serum PTH, creatinine, calcium, phosphorus, albumin, and H measurements,

which were performed using standard kits. Corrected calcium and Ca x P product were calculated using appropriate formulas. All patients underwent 2D-Echo for the measurements of PAP, IVS. CO was estimated from the left ventricular outflow tract velocity time integral x diameter. PAP above 35 mmHg was considered as high.For statistical analysis, descriptive data were expressed as mean + standard deviation (SD) and as frequency distributions. ANOVA was used to evaluate the linear relationship between pairs of variables and t-test for the relationship between mean values. The regression results were expressed using the partial correlation coefficient(r). All statistical analyses were performed using SPSS. Statistical significance was set at p value<0.05.

Results

The total number of HD patients in our unit was 149, of them 18 patients were excluded as they did not meet the requirements of the study, while the remaining 131 patients (76(58%) male, 55(42%) female) consisted of 64 diabetic and 67 nondiabetic patients were included in the study [table I].The mean age of patients was 53.7 + 16.2 yrs, ranging from 15-89 yrs. The mean duration on HD was 3.9 + 4.6 yrs.The mean PAP was 35.9+9.4mmHg (range 24-79mmHg).PH (PAP=47+3, range 35-79mmHg) was detected in 52 patients (39.6%) while the remaining 79(60.4%) have normal PAP (<35mmHg, range 24-34mmHg). Serum iPTH was 541.5 + 617 pg ml (range 9-2800pg ml). The means of serum calcium and phosphorus were 8.6 + 0.91 and 6.6 + 1.4 mg/dl respectively. The mean CO was5.9+ 1.2 L/min and the mean of IVS was 1.2 + 0.4 mm [table I]. The present study revealed a statistically significant direct correlation between the level of PAP and age (r =+0.190. P=0.04), MAP (r = +0.306, p=0.002), duration on HD (r =+0.246, P= 0.03), IVS (r =+0.223, P= 0.032) iPTH (r =+ 0.326, p= 0.0015), Creatinine (r = +0.153, P= 0.046) , Phosphorus (r =+0.292 , p=0.0025), Ca x P product(r =+ 0.245,p=0.03),and CO(r=+0.216,P=0.035). On other hand calcium and Hb levels were inversely correlated to levels of PAP (r = - 0.393, P = 0.001 and r= - 0.254, p=0, 029 respectively) [table II].

Furthermore, making a comparison between the data of PH patients with those in patients without PH we found that patients with PH have significantly higher levels of PAP, phosphorus, Ca x P product, creatinine, IVS, MAP, CO, duration of HD, and age (P<0.05) while the levels of serum calcium and Hb were significantly lower in PH group [table III]. On other hand, this study showed that history of diabetes mellitus(DM) and male gender inversely but not significantly affect PAP levels, p>0.05 [table IV].

Table I: Demographic and clinical data of patients.

Patients Data	**Values**
Number of study patients **Male / Female**	**131** **76/55**
PAP(mmHg)	**35.9±9.4(range 24-79)**
PTH (pg/ml) **Mean** **Range**	 **541 ± 617** **9 - 2800**
Ca – ((mg/dl)	**8.6 ± 0.9**
Phosphorus(mg/dl)	**6.6 ± 104**
CO	**5.9±1.2 l/min**
IVS(mm)	**1.2 ± 4**
AGE (yrs)	**53.7 ± 16.2**
MAP(mm Hg)	**99 ± 135**
PAP(mm Hg)	**35.9±9.4**

Table II: The significance of clinical data of thepatients in correlation with PAP levels.

Patients data	Pearson's correlation ®	P. Value
Age	+0.190	0.04
Calcium	-0.393	0.001
Phosphorus	+0.292	0.0025
Creatinine	+0.153	0.046
IVS	+0.223	0.032
iPTH	+0.326	0.0015
CO	+0.216	0.035
Duration on HD	+0.246	0.03
MAP	+0.306	0.002
Hemoglobin	-0.254	0.0029

Ca x P product	+0.245	0.03

Table III: Clinical and Biochemical data in patients with PH and without PH

History of PH / Patient data	With PH	Without PH	P value.
Age (years)	60±15	48±12	**0.03**
Phosph. (mg/dl)	7.4±1.9	4.2±2.1	**0.032**
Creat (mg/dl)	12.3±4	8.1±2.1	**0.023**
iPTH (pg/ml)	730±520	350±270	**0.01**
CO (L/min)	6.9±1.8	5.5±0.7	**0.021**
Duration on HD (years)	8.9±502	4.9±3.2	**0.01**
MAP (mmHg)	110±120	90±70	**0.02**
Hb (g/dl)	8.3±1.4	10.5±1.3	**0.04**
Ca x P Product	61±24	46±19	**0.037**
IVS (mm).	1.3±3	0.9±2.1	**0.035**
Ca (mg/dl)	7.2±1.1	8.9±.2.1	**0.04**
PAP (mmHg)	47±3.1	28±4.1	**0.001**

Patient's Data		PAP(mmHg),mean+ sd	P value
DM	Yes (n-64)	34.7±6	0.51
	No (n – 67)	36.5±9	
Gender	Male n-76	35.6±9	0.57
	Female n-55	37.4±8	

Table IV: The effect of gender and DM on PAP level

Discussion;

By our best knowledge, HD population in Jordan was scarcely investigated for pulmonary hypertension.

The present study, therefore, was conducted in order to continue the national efforts and to preclude for further studies in this important aspect of care in patients with ESRD. As in many other studies held worldwide (1, 5, 7, 9), the results of the present study indicate very high levels of PAP and high prevalence of PH in HD population. In this study we observed also very high levels of parathormone in addition to a strong correlation of PAP levels with PTH and mineral levels. On other hand hemoglobin (Hb) levels were inversely related to PAP. The comparison of the clinical and metabolic variables of PH patients and those without PH showed that patients with PH had significantly higher levels of PAP, PTH, phosphorous, P x Ca product, CO, IVS, MAP and longer duration on HD, but they had lower levels of Ca and Hb.

Based on the above mentioned data we suggest that anemia, mineral disorders, SHPTH, and increased CO as possible initiating processes in the development of PH and likely other cardiovascular diseases in the setting of ESRD. These important data mandate an immediate prevention and treatment of anemia and SHPTH . In this regard, the implementation of new therapeutic modalities, such as vitamin D2 analogues and calcimimetics and parathyroidectomy (8, 9, 13-17)

in addition to erythropoietin may be some of the resolutions.Along with high levels of PAP, in the present study we observed high levels of creatinine, in addition to significant positive correlation between PAP and creatinine levels, predicting the association of HD efficacy with the levels of PAP. In this regard it is important to use the more effective HD regimens in order to achieve dry weight reduction, improve kidney status, and decrease PAP (9, 17). The evaluation of these regimens in our dialysis units is still needed.Studying some of the international literature, there is a large controversy regarding the subject of our study. In concordance with our study, some studies suggested an increased blood flow due to anemia as an important process in the pathogenesis of PH (18), while other studies could not assess the relation between anemia and PH (19). On other hand, chronic hyperparathyroidism is associated with increased calcium content. Therefore, it is a possible cause of PH secondary to pulmonary artery calcification. One study showed obvious direct correlation between PTH activity and PAP levels and the authors suggested a link between PH and SHPTH ((8) .Other studies revealed no difference in levels of PTH, Ca, Phosphorus, and alkaline phosphatase in patients with and without PH (9). Finally, we believe that the failure of our HD unit to achieve the accepted levels of PAP has many reasons, including: - First: inadequate treatment of anemia and SHPTH. Second: the conventional regimens of HD, used in our unit, may be responsible for this failure. Third:parathyroidectomy was not performed in any of our patients despite high levels PTH.

Conclusion;

Along with the significant correlation of PAP levels with Mineral imbalance, anemia and cardiovascular abnormalities, very high levels of PAP were observed in our study population. This mandates an immediate revision of the management of CKD in general and PH in particular. Early diagnosis and treatment of anemia and SHPTH along with more effective HD regimens may be some of the resolutions.
Further multicenter and multidisciplinary studies of PH and its correlates are mandatory in Jordanian HD population.

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