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PULMONARY HYPERTENSION IN CHRONIC KIDNEY DISEASE - EPIDEMIOLOGY, CONSEQUENCES, AND ASSOCIATED FACTORS

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ABSTRACT

Pulmonary hypertension is a prevalent clinical condition in chronic renal patients can be present since the early stages of chronic kidney disease and several studies have correlated pulmonary hypertension with increased morbidity and mortality at different stages of chronic kidney disease, including post-transplantation. In chronic renal patients there are many possible causes because is high prevalence of left ventricular hypertrophy, diastolic dysfunction and left ventricular dysfunction resulting elevated left atrial pressures that would passively lead eventually pulmonary venous hypertension. Verified in this search a pooled prevalence PH was 36.3+/-10.5% hemodialysis and 20.7+/-8.8% CKD non dialysis. The principals associated factors were progressive with worsening renal function associated or not with cardiac dysfunction, hyperparathyroidism, hypervolemia and vascular calcifications.

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INTRODUCTION

Pulmonary hypertension is a prevalent clinical condition in chronic renal patients. It is a multifactorial disorder that affects patients from the early stages of chronic kidney disease (CKD). Its diagnosis is confirmed by systolic mean arterial pulmonary pressure is higher than 20 mm Hg at rest and pulmonary vascular resistance is greather than or equal to 3 woods units, via catheterization of the right cardiac chambers (Simonneau *et al*. 2019; Calderaro *et al*. 2019). However, echocardiography has been widely used in clinical practice being the best non-invasive screening test for PH (but does not establish a precise definition between different types of PH). Estimates pulmonary artery pressure using the measurements right atrial pressure and tricuspid valve systolic velocity measurements are classified as follows: normal (< 35 mm Hg); mild (35-43 mm Hg); moderate (45-60 mm Hg); and severe (> 60 mm Hg) (Sise *et al*. 2013; Lentine *et al*.2017). The identification of elevated pulmonary artery pressure in preclinical heart failure with preserved ejection demonstrates that echocardiography should be routine for these patients already in the early stages of CKD. Several studies have correlated pulmonary hypertension (PH) with increased morbidity and mortality (O'Leary *et al*. 2017; Bolignano *et al*. 2015;Reque *et al*. 2016) at different stages of chronic kidney disease, including post-transplantation (Tang *et al*. 2018). The Jackson Heart Study, performed with chronic renal African Americans, showed that individuals with pulmonary hypertension had more hospital admissions and mortality from heart failure in a period of approximately 7 years. That was a

pioneer study in analyzing CKD stage 2 to 4 patients (Selvaraj *et al*.2017). In a recent meta-analysis of 16 studies covering approximately 7112 patients at different stages of CKD, the authors correlated pulmonary hypertension (PH) with an increased relative risk of cardiovascular mortality, being higher in stage 5 CKD patients undergoing hemodialysis and peritoneal dialysis (RR 2.38 / RR 2.17 / RR 2.45) (Reque *et al*. 2016; Greeen *et al*. 2014; Agarwal 2012) and lower in the early stages of CKD (RR 1.38)(Navaneethan *et al*.2015). In chronic renal patients, pulmonary artery pressure may arise from many factors. These patients have high prevalence of left ventricular hypertrophy, diastolic dysfunction, and left ventricular dysfunction, resulting in elevated left atrial pressures that would passively lead to increased pulmonary pressure and eventually pulmonary venous hypertension. Decline in renal function is associated with increased volume overload and anemia, leading to a persistent increase in venous pressure(Navaneethan *et al*.2015). Clinical presentation includes asymptomatic cases to fatigue, dyspnea, chest pain, tachycardia, or overlapping heart failure (Salerno *et al*. 2017)

Pulmonary hypertension may occur in precapillary (resistance arteries) and postcapillary pulmonary vasculature (passive venous congestion). In most studies that verified this distinction through right chamber catheterization, the most prevalent type of PH in the chronic kidney is postcapillary due to venous congestion and left chamber dysfunction.[13](Pabst *et al*. 2012) Nevertheless, the precapillary type, which depends on vascular resistance obstruction, is also present. This type is associated with chemical mediators of vasoconstriction, such as endothelin-1 and ADMA, present in uremic patients (Sise *et al*. 2013). There is also the possibility of small pulmonary embolic events associated with hemodialysis (Barak *et al*.2008). The prevalence of PH in the chronic renal population varies according to the criteria used for diagnosis (catheterization, echocardiography), the stage of kidney disease (most prevalent with worsening renal function), the type of renal replacement therapy modality (higher prevalence in patients undergoing hemodialysis compared to peritoneal dialysis and kidney transplantation), and associated comorbidities (heart disease, anemia, vascular calcifications). Epidemiological studies indicate that PH may be present in 9-39% of CKD patients undergoing conservative treatment, 18-68.8% of hemodialysis patients, and 0-42% of peritoneal dialysis patients (Li *et al*. 2019).

Etiology in chronic kidney disease: There are many causes for increased pulmonary artery systolic pressure in patients with chronic kidney disease. These include: left ventricular hypertrophy and diastolic dysfunction (conditions highly prevalent in this population), endothelial dysfunction (favoring increased pulmonary vascular resistance), vascular calcifications, intravascular volume overload, sleep disorders, severe anemia, and arteriolar narrowing.(Li *et al*. 2019) Metabolic and hormonal disorders of uremia decrease pulmonary vasculature compliance, leading to endothelium-dependent vasodilation deficiency. There is an imbalance between vasodilators - such as prostacyclins and nitric oxide - and vasoconstrictors - such as endothelin, asymmetric dimethylarginine plasma (ADMA), and thromboxane (Sise *et al*. 2013; Briet *et al*. 2012; Genctoy *et al*. 2015). This review analyzes the main risk factors associated with pulmonary hypertension (PH) in chronic renal patients at different disease stages.

MATERIALS AND METHODS

Medical subject headings (MeSH) were used to search original articles and reviews through the MEDLINE and PubMed databases (NCBI, Bethesda MD, USA). The following search terms were used: “pulmonary hypertension” and “kidney diseases” OR “hemodialysis” OR “dialysis” OR “ckd non dialysis” and “echocardiogram”. The search was restricted to full manuscripts published in English. Abstracts for oral presentations, case reports, and letters to the editor were ignored. We also searched for further relevant articles in the reference lists of articles: Epidemiology, consequences, and associated factors. A total of 152 complete articles published between 2005 and 2019 were identified. First, titles and abstracts were read to know whether they fit the purpose of reviewing the issue. Then, 19 articles were selected and classified in tables according to the population studied.

Mild-severe chronic kidney disease in nondialysis patients: A wide range of renal dysfunction involves this group of patients at early stages of renal disease, such as stage 1 and 2 (only hematuria or proteinuria with normal glomerular filtration rate), and patients with major dysfunction, such as predialysis patients. This reflects the heterogeneity of CKD and its complications, more prevalent in later stages. Table 1 shows the prevalence of pulmonary hypertension and associated risk factors in nondialysis patients with chronic kidney disease in the years 2005 to 2019. A meta-analysis published in 2018 showed that in most studies on nondialysis chronic renal failure, pulmonary hypertension was present in 1/3 of the patients. It should be noted that the most studies refer to the estimate of pulmonary artery pressure verified by echocardiogram. Moreover, 21 articles published between 2007 and 2013 showed a PH prevalence of 7 to 24% in stage 1 and 2 patients, 8 to 66% in stage 3 patients, 15 to 49% in stage 4 patients, and 8 to 69% in stage 5 patients.[18](Shang *et al*. 2018) In another study with chronic renal patients undergoing conservative treatment, the prevalence was 35.9%, with a mean eGFR of 39.6 ± 13.6 ml/min. In that study, the pressure pulmonary artery was estimated by echocardiogram and was associated with older patients, lower ejection fraction, and hyperparathyroidism.[17](Genctoy *et al*. 2015)

Similar data were obtained from a retrospective Chinese study with patients at different stages of GFR, showing increased prevalence of increased pulmonary artery pressure (estimated by echocardiogram) in patients with hyperparathyroidism, lower hemoglobin, proteinuria, and higher BMI (Zhang *et al*. 2018). In another study, also based on a measuremet estimated by echocardiogram, PH prevalence increased with the decrease of GFR (2% stage 1 to 20% stage 5), associated age, systolic disfunction, diabetes mellitus, and cardiovascular mortality (Li *et al*. 2014). A retrospective cohort of about 30,000 chronic renal patients undergoing conservative treatment using echocardiographic parameters showed that the higher the pulmonary artery pressure, the greater the possibility of doubling creatinine and progressing to the need for renal replacement therapy. The researchers attribute the results to a greater impact of right ventricular dysfunction due to high venous pressures from increased hydrosaline retention in these patients (Mavrakanas *et al*. 2018). The kidney-lung relationship appears to be true, as demonstrated in an American study of 2368 patients with primary pulmonary hypertension.

Table 1. Prevalence of pulmonary hypertension and associated risk factors in patients with chronic kidney disease non dialysis

Study	Year	Population	Prevalence PH	Risk factors
Genctoy G et al [17]	2014	CKD non dialysis	35,9%	Lower ejection fraction and elevated PTH levels in patients with advances CKD
Li et al [20]	2014	CKD non dialysis	10%	Association with cardiovascular mortality according to severity, systolic dysfunction, age and diabetes mellitus
Selvaraj et al [7]	2017	CKD non dialysis	21,5%	Increased endothelin-1, tricuspid regurgitation, LVMI, increase left atrial diameter, increased B-typenatriureticpeptide
Bolignano D et al [4]	2015	CKD non dialysis	23%	Age, lower estimated glomerular filtration rate, enlarged left atrium and previous cardiovascular disease
Han BG e t al [24]	2019	CKD non dialysis	19,7%	Hypervolemia, pro-BNP increase
Zhang Q et al [19]	2018	CKD non dialysis	14,2%-64,4 (stage 1-5)	Elevated PTH levels, lower GFR, proteinuria, lower hemoglobin, higher BMI and triglycerides

CKD: chronic kidney disease; PTH: parathomone; LVMI: left ventricule mass index;
proBNP: pro brain natriuretic peptid; GFR: glomerular filtration rate;
AVF:arteriovenosous fistula; BMI: body mass index

Table 2. Prevalence of pulmonary hypertension and associated risk factors in patients in hemodialysis

Study	Year	Population	Prevalence PH	Risk factors
Nakhol F et al [28]	2005	Hemodialysis	39,7%	AVF, decreased nitric oxide
Mousavi et al [34]	2008	Hemodialysis	49,3%	Lower ejection fraction, lower serum albumin and lower hemoglobin
Fabbian F et al [27]	2010	Hemodialysis	58,7%	Elevated PTH levels, dialysis vintage, lower diastolic blood pressure, Lower ejection fraction, increased diastolic volume left ventricule
Paneni et al [32]	2010	Hemodialysis	NA	AVF
Zlotnick DM et al [51]	2010	Hemodialysis Pretransplant	38%	Increased risk to graft dysfunction, longer time on hemodialysis and deceased donor
Abedini M et al [25]	2013	Hemodialysis	31,6%	Age, smoking, systolic dysfunction and diastolic dysfunction
Kim SC et al [38]	2015	Hemodialysis	36,6%	Vascular calcification, increased left atrial diameter and mitral valvule disease
Genctoy et al [31]	2015	Hemodialysis	26,8%	Low Cholesterol, Low Albumin, Low body fat percentage
Yilmaz S et al [35]	2016	Hemodialysis	33,7%	Low albumin, low hemoglobin, female, fluid overload
Reque J et al [5]	2016	Hemodialysis	37%	Age, time on hemodialysis, systolic dysfunction, diastolic dysfunction, double mitral and aortic lesion, pro BNP increased
Foderaro et al [53]	2017	Hemodialysis Pretransplant	27%	Increased risk to graft dysfunction and deceased donor
Miri et al [36]	2018	Hemodialysis	22%	Decreasedserumcalcium
Wang SC et al [48]	2019	Hemodialysis Pretransplant	26,6%	Minor ejection fraction, right ventricular dilation, right ventricular hypertrophy, tricuspid regurgitation

PTH: parathomone; proBNP: pro brain natriuretic peptid;AVF:arteriovenosous fistula

Patients with a faster loss of renal function had higher morbidity and mortality, which interfered with the performance of a 6-minute walk test and with function. The authors suggest that eGFR may be used to follow up patients with pulmonary hypertension (Chakinala *et al*. 2018). A recent review of renal dysfunction in patients with pulmonary hypertension found a CKD prevalence of 4-36%. These two diseases share a wide range of inflammatory markers (TNF, IL6, angiotensin II, ADMA), in which PH therapies were considered nephroprotective (Nickel *et al*.2017). A Korean study of 137 nondialysis stage 5 CKD patients found a PH prevalence of 19.7%, being closely related to the hypervolemia of these patients evolving with increased pro-BNP levels. That study included echocardiography (using TRIv max > 2.9 m/s as criteria for pulmonary artery hypertension) and bioimpedance (Han *et al*. 2019).

Hemodialysis: A 2013 study analyzed patients in all renal replacement therapy modalities and found a higher prevalence of pulmonary hypertension in hemodialysis patients compared with peritoneal dialysis and kidney transplant patients. In addition, multivariate analysis showed a relationship between PH, age, smoking, systolic dysfunction, and diastolic dysfunction (Abendini *et al*. 2013; Santosh *et al*. 2019). A 2011 Italian study also found that PH (utilizing echocardiographics criteria) was more present in hemodialysis patients (58.7%) than in peritoneal dialysis patients (18.5%). In that study, PH was associated with hemodialysis duration and the lowest diastolic blood pressure (Fabbian *et al*. 2011). Table 2 shows the prevalence of pulmonary hypertension and associated risk factors in nondialysis patients with chronic kidney disease in the years 2005 to 2019. In hemodialysis, increased systoloic pressure of pulmonary artery may be associated with several factors such as systolic dysfunction (Reque *et al*. 2016; Abedini *et al*. 2013),hyperparathyroidism (Zhang *et al*.2018), arteriovenous fistula (Nakhoul *et al*. 2005; Yigla *et al*.2003),hemodialysis duration (Reque *et al*.2016; Fabbian *et al*. 2011), and inflammatory mediators (Yoo *et al*. 2017). There are still other less studied associations, such as those found in the study of Genctoy and collaborators (2014), who used bioimpedance in a sample of 179 patients. The authors found that nutritional parameters such as cholesterol, albumin, and body fat percentage were negatively correlated with pulmonary artery pressure (Genctoy *et al*. 2015), corroborating other studies that correlate mortality with malnutrition in the dialysis population (Paneni *et al*. 2010; Etamadi *et al* 2012). A study conducted in 2010 confirms findings from other studies on the association of PH and arteriovenous fistula in hemodialysis patients. In that study, however, there were no differences in AVF location (brachial or radial) (Etamadi *et al* 2012). Israeli researchers have analyzed the association of arteriovenous fistula and

pulmonary hypertension by means of a temporary AVF occlusion experiment with a sphygmomanometer. The authors observed a decrease in cardiac output and pulmonary artery pressure (Nakhoul *et al*. 2005). An Iranian study analyzed 61 hemodialysis patients, and lower hemoglobin, albumin, and ejection fraction were associated with increased pressure pulmonary artery, present in 49.3% of the subjects (Mousavi *et al*, 2008). Notwithstanding, a study with 77 HD patients correlated excess body water (verified by bioimpedance) with increased pulmonary artery pressure. In that study, increased pulmonary artery systolic pressure estimated by echocardiogram was found in 33.7% of the subjects and was associated with other factors such as albumin < 3.5 mg/dl, hemoglobin < 11 mg/dl, and female gender (Yilmaz *et al*.2016). A Spanish study analyzed 202 patients and found a PH prevalence of 37%, with a mean of 43 ± 11 mm Hg, being associated with older patients, longer hemodialysis duration, systolic and diastolic dysfunction, and double mitral and aortic lesion. Pro-BNP was three times more associated with PH than with non-PH subjects (Reque *et al*. 2016). In turn, an Iranian study of 50 patients (25 hemodialysis and 25 peritoneal dialysis) found PH to be present only in hemodialysis patients (22%), being associated with low calcium (Miri *et al*. 2018). Vascular calcification in chronic renal failure is a well-known complication in patients, especially in advanced stages of the disease. It is associated with increasing levels of parathyroid hormone (Sise *et al*.2013), impacting vascular remodeling and contributing to coronary artery disease and most likely to pulmonary artery bed calcifications (Allon *et al*. 2019). A study of 172 hemodialysis and peritoneal dialysis patients found an association between PH and vascular calcification score. However, there was no difference between the groups with and without PH regarding PTH levels, confirming that hyperparathyroidism contributes to vascular calcifications but is not the only mechanism involved in this process (Kim *et al*. 2015).

Conclusion

Pulmonary hypertension (PH) is a prevalent comorbidity in the patients studied, increasing with worsening renal function and conferring increased morbidity and mortality. It is associated with cardiac dysfunction, hyperparathyroidism, hypervolemia, and vascular calcifications. Although the majority of studies in chronic renal patients have defined pulmonary hypertension by echocardiographic criteria, it's emphasized that the definitive diagnosis must be made by the catheterization of cardiac chambers. Therefore, in addition to an echocardiogram, the treatment of chronic renal patients should include the analysis of pulmonary hypertension, indirect signs of hypervolemia, and atrial enlargement, emphasizing the importance of the cardio-renal-pulmonary axis.

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