

Original Paper

Cardiac, Inflammatory and Metabolic Parameters: Hemodialysis versus Peritoneal Dialysis

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Key Words

Left ventricular hypertrophy · Cardiothoracic ratio · Blood pressure · Inflammation · Mineral metabolism · Chronic kidney disease

Abstract

Introduction: Mortality in dialysis patients is higher than in the general population, and cardiovascular disease represents the leading cause of death. Hypertension and volume overload are important risk factors for the development of left ventricular hypertrophy (LVH) in hemodialysis (HD) and peritoneal dialysis (PD) patients. Other factors are mainly represented by hyperparathyroidism, vascular calcification, arterial stiffness and inflammation. The aim of this study was to compare blood pressure (BP) and metabolic parameters with cardiovascular changes [cardiothoracic ratio (CTR), aortic arch calcification (AAC) and LV mass index (LVMI)] between PD and HD patients. **Materials and Methods:** 45 patients (23 HD and 22 PD patients) were enrolled. BP measurements, echocardiography and chest X-ray were performed in each patient to determine the LVMI and to evaluate the CTR and AAC. Inflammatory indexes, intact parathyroid hormone (iPTH) and arterial blood gas analysis were also evaluated. **Results:** LVMI was higher in PD than HD patients (139 ± 19 vs. 104 ± 22 ; $p = 0.04$). In PD patients, a significant correlation between iPTH, C-reactive protein and the presence of LVH was observed ($r = 0.70$, $p = 0.04$; $r = 0.70$, $p = 0.03$, respectively). The CTR was increased in PD patients as compared to HD patients, while no significant differences in cardiac calcifications were determined. **Conclusions:** Our data indicate that HD patients present more effective BP control than PD patients. Adequate fluid and metabolic control are necessary to assess the adequacy of BP, which is strongly correlated with the increase in LVMI and with the increased CTR in dialysis patients. PD is a home therapy and allows a better quality of life, but PD patients may present a further increased cardiovascular risk if not adequately monitored.

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Introduction

Considering the reduced overall survival of patients with renal failure on dialysis, it appears clinically relevant to stratify the morbidity and mortality risk factors, with particular attention to cardiovascular risk [1, 2]. This is usually due to the presence of well-known conditions, such as arterial hypertension, diabetes mellitus, ageing and dyslipidemia, and to several complications, such as volume overload, uremic cardiomyopathy and vascular damage with arterial stiffness and vascular calcification [3–5]. The prevalence of hypertension in dialysis patients is particularly high. Mean arterial blood pressure (BP) and cardiovascular morbidity are strongly related [6, 7]. The Netherlands Cooperative Study on the Adequacy of Dialysis showed that systolic BP (SBP) is an independent predictor of mortality and an indicator of fluid overload in dialysis patients. In particular, two specific causes of hypertension are often present: increased arterial stiffness and fluid overload [8–11]. Hypertension and hypervolemia can result in an increase in the left ventricular (LV) afterload and may lead to an increase in LV wall thickness, although this condition alone fails to explain LV hypertrophy (LVH). Also, LVH is not always correlated with the severity of hypertension and hypervolemia in dialysis patients [3, 12–17]. Another possible cause of LVH may be the increased cardiac output state produced by high-flow arteriovenous fistula, or anemia, as well as the direct effect of hyperparathyroidism [16, 17]. A link between abnormalities of mineral metabolism and LVH has been previously described. In fact, intact parathyroid hormone (iPTH) exerts direct trophic effects on cardiac myocytes and fibroblasts resulting in intramyocardial arterial wall thickening, LVH and myocardial fibrosis [18–20]. These effects were shown by *in vitro* studies where PTH induced chronotropic, inotropic as well as hypertrophic effects on cardiomyocytes. In this light, Katoh et al. [21] and Saleh et al. [22] described a positive inotropic action played by PTH on the isolated papillary muscle of the rat heart with direct evidence of a hypertrophic effect of PTH. This condition was also shown on adult ventricular cardiomyocytes [23]. Furthermore, vascular calcification that accompanies secondary hyperparathyroidism (SHPT) in end-stage renal disease (ESRD) leads to an increased arterial resistance and induces the formation of LVH [24–26]. Other factors, such as oxidative stress, inappropriate activation of the renin-angiotensin-aldosterone system and inflammation, may also play a role in LV growth in ESRD [27]. Persistent activation of the inflammatory response has been recognized as an important independent risk factor for the development of cardiovascular complications in dialysis patients [28]. The pathophysiological mechanisms by which inflammation might contribute to the development of ventricular hypertrophy are still not completely understood. Inflammation may promote the development of LVH by changes in the function and morphology of vascular smooth muscle cells that increase arterial stiffness [27, 28]. Additionally, subclinical inflammation can lead to LVH by altering the equilibrium that regulates cell growth, apoptosis, phenotype and matrix turnover of cardiac tissue. However, it was shown that inflammation predicts future increase in BP, suggesting that increased inflammatory state may precede the increase in BP [29]. Assessment of these conditions and constant research on new serum blood markers and instrumental parameters in patients with ESRD appear mandatory to reduce the high cardiovascular morbidity and mortality [30, 31].

The cardiothoracic ratio (CTR) is an easily available parameter from routine posterior-anterior chest radiographs. It usually indicates the LV size and may provide reasonable estimates of vascular calcification [32].

The aim of this study was to compare BP and metabolic parameters with cardiovascular abnormalities [CTR, aortic arch calcification (AAC) and LV mass index (LVMI)] between a group of peritoneal dialysis (PD) and a group of hemodialysis (HD) patients.

Materials and Methods

Study Design

We performed an observational study, between October 2009 and April 2013, on 45 clinically stable patients on a dialysis program at the University Hospital 'Policlinico Umberto I' of Rome, Sapienza University of Rome, Italy. The sample size is based on similar experiences from studies conducted in only one single center [33, 34].

The study protocol was approved by the local ethics committee. The study conforms with the principles outlined in the Declaration of Helsinki.

Patients

Inclusion Criteria. We included consecutive patients aged ≥ 18 years with stable clinical and biochemical conditions in a HD or PD program for at least 3 months.

Exclusion Criteria. Patients who refused to give consent for participation were excluded. Patients with underlying malignancy, hepatic insufficiency or alcoholism, chronic obstructive pulmonary disease, intercurrent acute illness and/or major infections and severe heart failure (ejection fraction $<35\%$) were not included. Patients with a technically inadequate image on echocardiography, the presence of hemodynamically significant valvular disease or pericardial effusion were also excluded.

Measurements

Clinical examinations of HD patients were performed during the middle of the week, before HD treatment, while PD patients were examined before the first replacement of the morning with an empty peritoneum. Height and weight were measured with the patient wearing indoor clothing before starting intraperitoneal dialysate infusions at routine visits. Body mass index (BMI) was calculated using the formula of [weight (kg)/height (m²)].

Laboratory Measurements. Blood was drawn in the morning after an overnight fast of at least 12 h, before HD treatment. In all patients, the levels of fasting plasma glucose, hemoglobin (mg/dl), hematocrit, calcium (mg/l), phosphorus (mg/l), total serum cholesterol (mg/dl), high-density lipoprotein (HDL; mg/dl), low-density lipoprotein (LDL; mg/dl), triglycerides (mg/dl), creatinine (mg/dl), urea nitrogen (mg/dl), albumin (g/dl), sodium (mEq/l), potassium (mEq/l) and C-reactive protein (CRP) were measured by standard automated techniques. Serum albumin (g/dl) was determined by the bromocresol purple method. PTH was determined by a two-site assay that measures 'intact' hormone. The calcium phosphate product was calculated using serum calcium concentrations, corrected for serum albumin concentration. Renal function was estimated using the MDRD (modification of diet in renal disease) formula. LDL cholesterol was calculated using the Friedewald equation: LDL (mg/dl) = total cholesterol – HDL – (triglycerides/5). Arterial blood gas analysis was performed by a blood gas analyzer (Nova Phox Plus C).

BP Measurements. Clinic BP measurements were made 3 times after 10 min of rest in a seated position using a standard sphygmomanometer and cuffs adapted to the arm circumference according to the British Hypertension Society guidelines, and the mean values for SBP and diastolic BP (DBP) were calculated for all participants. SBP and DBP levels were measured in PD and HD patients before and after the dialysis session at routine visits in a fasting state. The SBP and DBP levels were taken as the points of appearance and disappearance of Korotkoff sounds, respectively. Hypertension was defined by elevated SBP (>140 mm Hg), DBP (>90 mm Hg) and median arterial BP readings on repeated measurements and on different days.

X-Ray Measurements. Chest X-ray was used to evaluate the CTR, and it was performed before the HD session and in a fasting state for PD patients. We used technically adequate posterior-anterior chest X-ray, with defined borders and a defined heart aortic arch. Three adjudicators independently assessed technical adequacy, with disagreements resolved by consensus. Standard chest radiographs were taken in a standing position in the anterior-posterior view and the CTR was measured based on these radiographs. The CTR was calculated as the ratio of the maximum transverse cardiac diameter in millimeters to the maximum thoracic diameter in millimeters. We defined a normal CTR value as less than 0.5 [29, 30].

Assessment of Aortic Calcification Using Chest X-Ray. The grade of AAC using a previously validated scoring system was assessed: grade 0 (no visible calcification), grade 1 (small spots of calcification or single thin calcification of the aortic handle), grade 2 (one or more areas of thick calcification) and grade 3 (circular calcification of the aortic knob). All measurements of AAC and CTR were assessed independently by three adjudicators, with disagreements resolved by a consensus measurement [31, 32].

Echocardiography. Transthoracic echocardiography was performed before the HD session and after emptying the peritoneal cavity in PD patients. M-mode 2D echocardiographic examinations were completed by

Table 1. Baseline characteristics of the patients (n = 45)

Male n (%)	19 (42.2)
Age, years	64.5±12
Body weight, kg	67.4±12.5
Height, cm	167±8.5
BMI	23.7±2.7
Hb, g/dl	12.7±1.5
Glycemia, mg/dl	77.6±5.7
Creatinine, mg/dl	7.1±2.7
BUN, mg/dl	71±21.9
eGFR, ml/min	5.8±4.3
Sodium, mEq/l	141±2.2
Potassium, mEq/l	4.3±0.6
Calcium, mg/dl	9.1±0.5
Phosphorus, mg/dl	3.5±0.5
Ca × P, mg ² /dl ²	31.4±4.5
Total cholesterol, mg/dl	157.9±26.8
HDL, mg/dl	44.4±12.5
LDL, mg/dl	123.5±20.6
Triglycerides, mg/dl	135.1±50.6
Iron, µg/dl	77.6±29.3
Ferritin, ng/ml	117.3±80.1
Transferrin, mg/dl	258.3±46.5
Uric acid, mg/dl	4.3±0.9
CRP, mg/dl	0.2±0.1
Albumin, g/dl	4±0.7
APD	9
CAPD	13
HD	10
HDF online	5
AFB	8
Dialysis time, years	4.5±2.6

Data are shown as means ± SD or number (%). Hb = Hemoglobin; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; HDF online = hemodiafiltration online; AFB = acetate free biofiltration.

a single experienced sonographer in the echocardiography laboratory using a standard institutional protocol. Commercially available instruments (Toshiba Aplio xV, Toshiba American Medical Systems, Inc., Tustin, Calif, USA) equipped with 2.25- to 7.5-MHz imaging transducers were used; the subjects were in the left decubitus position, and the sonographer was blinded to all clinical details of the patients. All echocardiographic data were recorded according to the guidelines of the American Society of Echocardiography (ASE). The end-diastolic and end-systolic LV internal diameter, interventricular septum thickness and posterior wall thickness were measured. The LV mass (LVM) was estimated by Devereux's formula normalized by body surface area and height [35–38].

Statistical Analysis

Data management and analysis were performed using IBM® SPSS® Statistics 17 for Windows® software (IBM Corporation, Armonk, N.Y., USA). The normality of the variables was tested using the Shapiro-Wilk method for normal distributions. All continuous variables were expressed as means ± standard deviation and categorical variables were expressed as numbers (percentages). Student's t test, Mann-Whitney U test, and Fisher's exact test were performed to determine differences between groups, as appropriate. The binomial test or χ^2 test was used for comparison of categorical data. Pearson's or Spearman's correlation was applied to determine the relationship and the strength of the association between the variables in bivariate correlation. A probability value of $p < 0.05$ was considered statistically significant.

Fig. 1. Box-and-whisker plots. **a** SBP in PD patients versus HD patients. **b** DBP in PD patients versus HD patients. **c** Median arterial BP (MAP) in PD patients versus HD patients. • = Outliers.

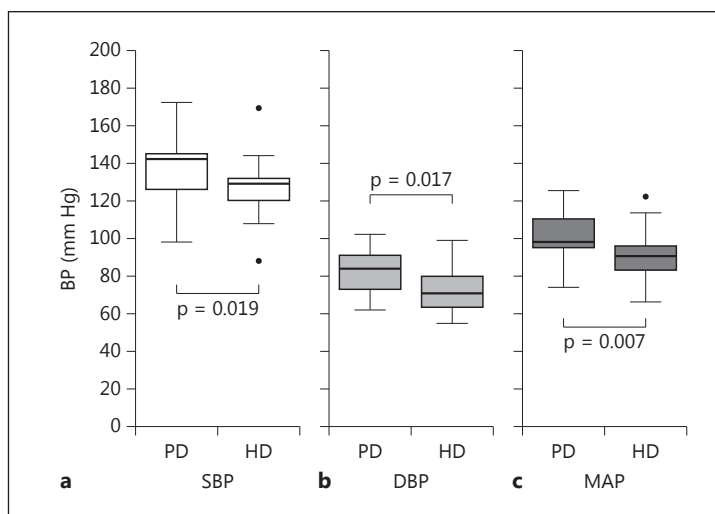
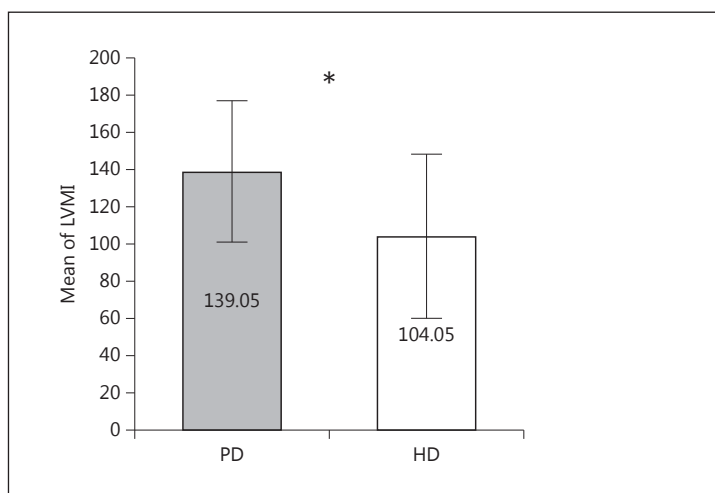


Fig. 2. Bar charts with error bars. The mean value of LVMI was significantly higher in PD patients compared with HD patients (* $p = 0.037$). Boxes represent means; error bars indicate ± 2 SD.



Results

Patient Characteristics

The study included 23 patients (9 males, 14 females) from the Hemodialysis Unit and 22 patients (10 males, 12 females) from the Peritoneal Dialysis Unit at our clinic. We enrolled the entire population of patients at our clinic to represent all the patients treated. The mean age of the 2 groups was 64.5 ± 12 years. The cause of ESRD was chronic glomerulonephritis in 10 patients, diabetic nephropathy in 9 patients, autosomal dominant polycystic kidney disease in 4 patients, hypertensive nephrosclerosis in 12 patients and unknown in 10 patients.

Table 1 shows the general characteristics of the study participants. In particular, 18 patients (7 on PD and 11 on HD) were taking antihypertensive drugs with a previously good BP control and 14 patients were smokers. Antihypertensive, antiplatelet and statin therapies were continued in the patients included in the study.

There were no statistically significant differences in age, sex, height, weight, BMI, serum sodium, potassium, calcium, phosphorus, $\text{Ca} \times \text{P}$ product, glucose, Hg, HDL, triglycerides, pH and concentration of bicarbonates between the groups. The mean values of SBP, DBP and median arterial BP were significantly higher in PD patients compared to HD patients ($p = 0.019$, $p = 0.017$ and $p = 0.007$, respectively; fig. 1) as well as the LVMI ($p = 0.037$; fig. 2).

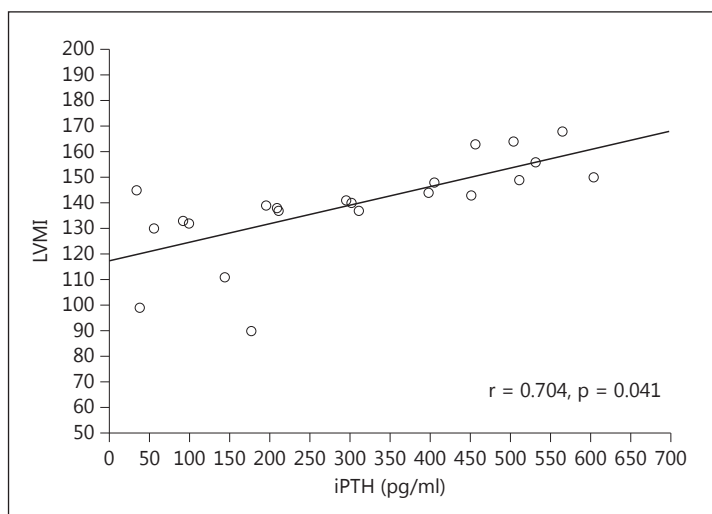


Fig. 3. Linear regression plot. LVMI versus iPTH in PD patients ($r = 0.704$, $p = 0.041$).

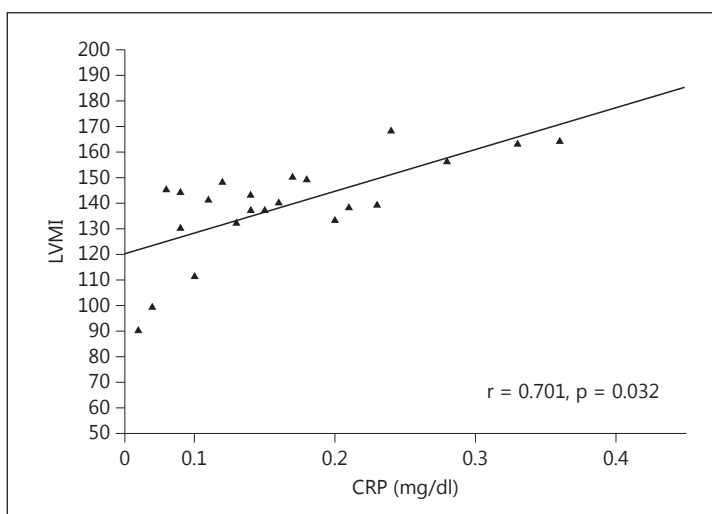


Fig. 4. Linear regression plot. LVMI versus CRP in PD patients ($r = 0.701$, $p = 0.032$).

A significant correlation was observed between iPTH, CRP levels and the presence of LVH in PD patients ($r = 0.70$, $p = 0.04$ and $r = 0.70$, $p = 0.03$, respectively; fig. 3, 4). However, no correlations of serum Ca or P with LVMI were obtained. Also, the CTR was increased in PD patients (CTR >0.5 in 15/22 PD patients; CTR >0.5 in 7/23 HD patients) ($p = 0.001$), but no significant correlations with AAC were observed.

Discussion

Although the use of dialysis procedures significantly improved the outcomes of ESRD patients, dialysis patients still die prematurely, being early cardiovascular disease the leading cause of death [1, 3]. Clinical studies have reported a high prevalence of cardiac abnormalities in dialysis patients, particularly the presence of LVH.

These cardiac alterations result from arterial hypertension and volume overload, associated with a number of metabolic and neurohormonal abnormalities. However, LVH is not always correlated with the severity of hypertension and hypervolemia [1, 3, 6, 9, 39].

In our study, the mean values of BP, LVMI and CTR were significantly higher in PD patients compared with HD patients. The greater frequency of arterial hypertension in PD patients may be due to the greater hydration state, considering that these patients are susceptible to extracellular volume expansion, and evidence indicates that PD patients have a greater fluid overload than HD patients [1, 3, 6, 16].

The absence of overt fluid retention in the physical examination is, by itself, insufficient to exclude significant hypervolemia. Clinically, dry weight is estimated by trial and error with less accuracy in the adjustment of dry weight, also due to the continuous changes in the peritoneal membrane [3, 6, 40, 41]. Adequacy of PD is traditionally assessed using K_t/V_{urea} and total creatinine clearance; however, this approach underestimates the importance of fluid overload [1, 3].

The bodily distribution of excess fluid is different between HD and PD patients. Overhydration in PD patients is mainly present in the subcutaneous tissue, while blood volume overload in HD patients is generally the cause of body weight gain during the interdialytic period (48–72 h), due to the consumption of foods and liquids, and of a reduction during the session (4 h) by a rapid ultrafiltration from the intravascular compartment and a slow ultrafiltration from the interstitial space through refilling. Usually, the PD technique is continually executed, and balance is obtained between the different compartments in a continuous way by the ultrafiltration from the interstitial space [6]. HD patients present a greater hydration state before the dialysis session, but it decreases after the session, with subsequent increases up to the next session, reflecting the changes in PD [42].

Moreover, many errors can occur in estimating LV volume or LVM because these parameters are influenced by volume overload and by body weight. Therefore, it appears essential to perform studies using echocardiography at the same time as the HD session [3]. We performed transthoracic echocardiography before the HD session, and after emptying the peritoneal cavity in PD patients. Also, patients undergoing automated PD, which has a higher fluid removal capacity than continuous ambulatory PD (CAPD), were only partially protected. In fact, in our study, no significant differences between patients treated with CAPD and patients on automated PD were observed.

Long-term CAPD is disadvantageous for the preservation of cardiac performance, and it is associated with the greatest LVMI compared to both short-term CAPD and HD [42]. In this light, several studies showed that long-term CAPD patients have a greater volume overload and more severe LVH than HD patients [38–40]. This may explain the higher prevalence of and more severe LVH observed in PD patients, with a mean time from the start of dialysis of 4 ± 2 years. This seems to be related to the reduction of the residual renal function that may also play a role in limiting the increase in LVMI by improving the removal of uremic toxins [43].

In addition to the effects of BP and volume, several nonhemodynamic factors influence LVM in dialysis patients. In fact, we also observed a correlation between iPTH, CRP levels, the CTR and the presence of LVH in PD patients.

The International Pediatric Peritoneal Dialysis Network (IPPN) registry collects detailed prospective clinical and echocardiographic information, which has recently been analyzed in detail and showed that hyperparathyroidism was independently associated with LVH. In addition to the well-known PTH target organs [44], PTH receptors have also been identified in the heart and in the vascular system, and in vitro, PTH induced hypertrophy of cardiomyocytes and arteriolar wall thickening [22].

The mechanisms by which PTH interacts on myocardial tissue, directly or indirectly, have been investigated in several models. Bogin et al. [45] showed in an experimental model that PTH causes a rise in heart rate. A similar finding was reported in 1993 by Wang et al. [46] indicating that PTH causes contraction in isolated ventricular myocytes from neonatal rats.

This result was also confirmed in a study performed on isolated papillary muscles of rat hearts [23]. Additionally, there is evidence of a hypertrophic effect of PTH on isolated cardiomyocytes from adult rats [22]. Furthermore, Amann et al. [24] showed that PTH seems to have a permissive role in fibroblast activation in nephrectomized and parathyroidectomized rats inducing intramyocardial fibrosis. Furthermore, SHPT may contribute to vascular dysfunction, with increased arterial stiffness, which may lead to persistent increases in BP [25].

Continuous activation of the inflammatory response is an important independent risk factor for the development of cardiovascular abnormalities in dialysis patients. Wang et al. [28] showed that chronic microinflammation, through its association with progressive atherosclerosis, participates in the maintenance of hemodynamic overload limiting the efficacy of therapeutic interventions [27]. Recent studies reported an inverse relationship between CRP and other inflammatory mediators and renal function, suggesting that uremia per se may contribute to the inflammatory response, although the exact mechanism is not completely clear [47]. In this light, in murine models altered TNF and IL-1 clearance was described in nephrectomized rats [48].

In our study, an independent association was observed between CRP and LVH in PD patients, but the exact mechanism of this association is not clear. CRP may be considered as a marker of LVH or of the increased inflammatory state, and LVH may be correlated to the presence of volume overload. Indeed, volume overload is a frequent complication in PD patients and is itself associated with immune activation leading to an increased production of proinflammatory cytokines [28]. Volume overload can worsen arterial hypertension, which is associated with more severe LVH. Thus, volume overload may in part explain the association between inflammation and LVH. However, some studies have shown that inflammation may precede the increase in BP. Inflammation and SHPT may promote arterial stiffness that contributes to LVH and cardiomegaly. In fact, the CTR significantly correlates with CRP and LVH in PD patients. It is an easily available parameter from a routine posterior-anterior chest radiograph that usually indicates the LV size and may provide reasonable estimates of vascular calcifications. Although cardiomegaly lacks specificity in identifying the cardiac lesion, its presence has a strong prognostic significance in patients with a high cardiovascular risk.

Gao et al. [49] reported that Δ CTR is an important prognostic factor in PD patients. In our study, the CTR was increased in PD patients. PD appears to have clear advantages, considering the possibility of performing the treatment at home, improving patients' quality of life. Surprisingly, only two studies comparing the quality of life of HD and PD patients are available: the North Thames Dialysis Study [50] and Broadening Options for Long-Term Dialysis in the Elderly (BOLDE) [51]. The survival rate, however, is usually longer in HD patients, especially in older diabetic patients. Vascular access, intradialytic hypotension, which may relate to myocardial dysfunction, and impaired autonomic function with hemodynamic instability, bleeding and amyloidotic arthropathy represent the most critical aspects of HD treatment. Furthermore, we should consider that PD is a less expensive treatment than HD [52, 53]. However, PD patients should be constantly monitored with clinical and instrumental tools, including bioelectrical impedance, CTR and echocardiogram, since they are at increased risk of developing volume overload and cardiovascular disorders [54], as confirmed by the present study. Larger clinical trials are needed to confirm our results.

Limitations

Our study presents a relatively small, selective cohort of HD and PD patients, and the lack of correlation in the HD group may be due to the small sample size. Therefore, a larger population is warranted. Also, our study is based on associations with surrogate end points; the

generated hypothesis needs further prospective follow-up studies with stronger end points to show causality. Furthermore, as shown in our results, a significant proportion of the patients were on antihypertensive and statin therapies and they were smokers. In this sense, the potential impact of hypertension, hypercholesterolemia and their treatments may have possibly confounded the results.

Conclusion

Arterial hypertension and LVH are important clinical features in PD patients. Adequate fluid control to assess the adequacy of BP control is necessary, and it is well correlated with the increase in LVMI and CTR in PD patients. HD patients have a better control of BP with a significantly lower LVMI compared to PD patients. Other factors such as hyperparathyroidism and inflammation may also play a role in LVH. The CTR is easily obtainable by chest radiography and correlates with inflammation and LVH.

Further elucidations on the etiology of cardiomegaly and on the presence of calcifications are necessary and may require second-level surveys with the use of echocardiography and/or cardiac CT scan.

Disclosure Statement

The authors have no conflicts of interest to declare.

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