Chapter 5

The Association with Cardiovascular Events and Residual Renal Function in Peritoneal Dialysis

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Additional information is available at the end of the chapter

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1. Introduction

Life expectancy among the patients with chronic kidney disease (CKD), especially among the ones with end-stage renal disease (ESRD) has decreased that is significantly lower than the general population. The leading cause of morbidity and mortality among the dialysis patients with ESRD are cardiovascular disease (CVD) which are reported to be responsible of a 50% mortality rate in these patients [1].

The prevalence of traditional cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes, physical inactivity is higher in dialysis patients. Besides these, there are uremia-specific, nontraditional risk factors, including volume overload, anemia, disordered mineral metabolism, increased inflammation and oxidative stress, and malnutrition, all of which are associated with higher all-cause and cardiovascular mortality in dialysis patients. Cardiovascular risk factors that are unique to peritoneal dialysis (PD) patients, including residual renal function (RRF), peritoneal membran integrity, infection, dialysis center size, patient education and training, all of which are also associated with higher all-cause and cardiovascular mortality in dialysis patients.

In 1995, Maiorca et al were among the first to note an independent relationship between the presence of residual renal function, and survival in patients on dialysis [2]. Several subsequent studies reported similar findings that residual renal function but not the dose of peritoneal dialysis was a powerful predictor of survival in peritoneal dialysis patients [3-7].

The mechanism underlying survival benefits associated with RRF in PD patients is not clear. RRF has been implicated to be important in maintaining the fluid balance of patients on PD. RRF also plays an important role in phosphorus control, and removal of middle molecular uremic toxins. In addition, loss of RRF is associated with higher arterial pressure, more severe

anemia, greater degree of inflammation and malnutrition, and greater cardiac hypertrophy, all of which contribute to increased cardiovascular events in peritoneal dialysis patients.

The Framingham Study showed the relationship of left ventricular hypertrophy (LVH) with higher cardiovascular mortality in general population [8]. Studies showed that prevalence of LVH is higher among dialysis patients [9,10]. The severity of left ventricular hypertrophy, a strong independent predictor of mortality in patients on dialysis, inversely correlates with the presence of RRF [10]. LVH may cause cardiovascular events, such as congestive heart failure, arrhythmia, and sudden cardiac death in dialysis patients [11,12].

This chapter will review the association with cardiovascular events and residual renal function in patients on peritoneal dialysis.

2. Measurement of residual renal function

Residual renal function represents the function of the native kidneys or the in situ kidney allograft [13]. RRF may be measured or estimated. Residual GFR measured by isotope clearance is considered to be the standard measure of renal function. Other tests, such as serum creatinine, creatinine clearance, urea clearance, an average of the creatinine and urea clearances, and urine volume have been used to evaluate RRF in chronic kidney disease. The simplest measure of RRF is urine volume. Despite its shortcomings, urine volume has been correlated to GFR in studies, and most authors defined loss of RRF as estimated urine volume ≤ 200 mL/24 hour.

NKF-K/DOQI and European guidelines currently recommend that mean urea and creatinine clearance be used for PD patients [13,14]. Urine collections (24 hours for PD, interdialytic for HD) to measure urea and/or creatinine clearance could be done at baseline and every 1 to 3 months in patients with RRF.

3. Cardiovascular disease in peritoneal dialysis patients

Although dialysis technology has improved markedly over the last 20 years, dialysis patients still die at a rate of about 10–20% per year – a survival worse than that documented in patients with cancer disease [1]. Early studies observed that morbidity and mortality rates were lower in HD patients [15]. However, further studies discovered that PD could achieve patient survival that was the same or better than that with HD [16-18].

Among dialysis patients, cardiovascular disease is common, with similar cardiovascular mortality rates in a 20-year-old dialysis patient and an 80-year-old member of the general population. CVD including ischemic heart disease, left ventricular hypertrophy, heart failure, arrhythmia and sudden cardiac death, accounts for most deaths in dialysis patients (approximately 50%). Even though accelerated atherosclerosis seems to be an important cause of the high cardiovascular mortality in dialysis patients, the CVD pattern is atypical and a lot of non-

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traditional risk factors, such as volume expansion, anemia, inflammation, oxidative stress, malnutrition, disordered mineral metabolism, sympathetic overactivity, and loss of residual renal function contribute to the high cardiovascular mortality rate. The data of the United States Renal Data System (USRDS) registry show that cardiac arrest/arrhythmia is the major cause of cardiovascular death in this patient population [1].

Ischemic heart disease may be suboptimal diagnosis and treatment because atypical clinical manifestations in dialysis patients. Heart failure rates are also extremely high and commonly presents specific symptoms. Among the cause of deaths are cerebrovascular disease and peripheral vascular disease in dialysis patients. Arrhythmias are also extremely common in dialysis patients, most likely reflecting the prevalence of structural heart disease, ischemic heart disease, and electrolyte abnormalities.

LVH is the most prominent structural cardiovascular alteration in dialysis patients. LVH is defined as the increase in myocard fibrils and in the mass of left ventricle muscle that generally emerges as a result of a volume or pressure load [19]. There are two kinds of LVH one of which is concentric hypertrophy due to excessive pressure load and the other is eccentric hypertrophy due to volume load on left ventricle [20]. Diagnosis of LVH is readily accomplished with echocardiography in patients with symptomatic or asymptomatic cardiac diseases. A study demonstrated that 74% of ESRD patients have LVH [9]. In another study was showed that 92% of PD patients have LVH [10]. It was reported that in dialysis patients, high left ventricular mass index and cavity volume were independently associated with death after two years [9]. It was also reported that there is a tendency of heart failure or early death for the dialysis patients that have presence of LVH at the beginning of the therapy. Authors concluded that potentially reversible risk factors include anaemia, hypertension, hypoalbuminaemia and ischaemic heart disease [20].

In a prospective study in 161 dialysis patients were tested the prognostic value of changes in left ventricular mass index (LVMi) [expressed as LVM/height$^{2.71}$], on survival and incident cardiovascular events. In this purpose, echocardiography was performed twice, 18 +/- 2 SD months apart. It was found that the rate of increase of LVMi was significantly higher in patients with incident cardiovascular events than in those without such events. In their multiple Cox regression analysis, (including age, diabetes, smoking, homocysteine), showed that 1 g/m$^{2.7}$/month increase in LVMi was associated with a 62% increase in the incident risk of fatal and nonfatal cardiovascular events. Author concluded that changes in LVMi have an independent prognostic value for cardiovascular events and provide scientific support to the use of repeated echocardiographic studies for monitoring cardiovascular risk in dialysis patients [11].

A prospective study was performed by Foley et al, in eastern Canada. In 432 dialysis patients, they showed that a lowering of cardiac size and an increase in fractional shortening over a 1-year period after inception of dialysis therapy were both associated with a reduced subsequent likelihood of cardiac failure. They suggested that the associations between serial change in both left ventricular mass index and fractional shortening and subsequent cardiac failure persisted after adjusting for baseline age, diabetes, ischemic heart disease, and the corresponding baseline echocardiographic parameter. Regression of left ventricular abnormalities is associated with an improved cardiac outcome in dialysis patients [21]. In another study by

London et al. demonstrated that 10% decrease in left ventricular mass of dialysis patients leads to 28% decrease in the mortality caused by cardiovascular events [22].

Several mechanisms may contribute to explain the increased cardiovascular risk associated with LVH. LVH is associated with myocardial fibrosis, systolic and diastolic dysfunction which is an important factor in the evolution of cardiac arrhythmia and heart failure. Furthermore LVH reduces coronary reserve and induces cardiac ischemia which may in turn promote myocardial infarction and lethal arrhythmias [11]. In addition to it was showed that there is the link between uremic cardiomyopathy, QT interval and dispersal, and arrhythmias in chronic kidney disease patients [23]. It was suggessted that arrhythmias due to the abnormal electrical conduction of fibrotic ventricles can become the leading cause of mortality in dialysis patients by resulting in sudden cardiac arrest.

In summary, concentric and eccentric left ventricular hypertrophy are common and progressive disorders in dialysis patients and are associated with cardiac ischemia, cardiac failure, arrhythmias and sudden cardiac death.

4. Survival benefits of residual renal function in peritoneal dialysis

Studies have been demonstrated that the presence of RRF is associated with survival in both PD and hemodialysis (HD) patients. As mentioned above, in 1995, Maiorca et al were among the first to note an independent relationship between the presence of RRF and survival in patients on dialysis [2]. In their analysis of 102 patients on PD and HD, every 1-mL/min increase in glomerular filtration rate (GFR) was associated with a 40% reduced risk of death in the entire cohort and a 50% reduced risk of death in patients on PD.

In a prospective observational study it was performed in 1446 PD patients and weekly Kt/V urea and creatinine clearance were determined at study baseline. During the seven month period of follow-up, there were 140 deaths. It was reported that in separate logistic regression models that included all of the studied risk factors, using separate variables for the urinary and peritoneal components of dialysis adequacy, each 10 L/week/1.73 m^2 increase in the urinary component of weekly creatinine clearance was associated with a 40% decreased risk of death, and each 0.1 unit increase in the urinary component of weekly Kt/V urea was associated with a 12% decreased risk of death. In contrast, the dialysate components of neither weekly creatinine clearance nor weekly Kt/V urea were predictive of death. Other factors that were associated with an increased risk of death included increasing age, diabetes mellitus as the cause of end-stage renal disease, and a history of myocardial infarction. Authors concluded that residual renal function is an important predictor of death in peritoneal dialysis patients [3]. Another study it was conducted in 1603 PD patients. Similarly, the analysis of clearance data or peritoneal equilibration test (PET) studies also confirmed residual renal function was strongly correlated with survival, but peritoneal clearance was not [4].

Reanalysis of data from the multicenter prospective cohort Canada–United States (CANUSA) study of 680 incident patients on PD demonstrated that for each 5 L/wk per 1.73 m^2 increment

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in residual glomerular filtration rate (rGFR), there was a 12% decrease in the relative risk of death but no association with peritoneal creatinine clearance. It was suggested that the predictive power for mortality in patients on PD was attributed to RRF and not to the dose of PD. Moreover it has reported that low residual renal function at start of peritoneal dialysis is associated with increased mortality in patients with end-stage renal disease [5].

Similar results were found in The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD-2), in which each 1-ml/min increase in rGFR was associated with a 12% reduction in mortality, and peritoneal clearance had no significant effect on patient survival [6].

ADEquacy of Peritoneal Dialysis in MEXico (ADEMEX) study lent further important evidence that residual renal and peritoneal dialysis clearance are not equivalent and thus not simply additive. In this prospective randomized controlled study, increasing peritoneal clearance showed no additional impact on the survival of either all patients or anuric PD patients, but the presence of RRF has a beneficial effect on patient survival [7].

These findings has been shown that the contribution of residual renal and peritoneal dialysis clearance to the survival of peritoneal dialysis patients is not equivalent. It was also suggested that preservation of RRF has an important role in the survival of peritoneal dialysis patients.

The mechanism underlying survival benefits associated with RRF in peritoneal dialysis has been drawn very much attention. The details will be discussed in further sections.

5. Risk factors of cardiovascular disease in peritoneal dialysis patients

Dialysis patients have a high prevalance of traditional (Framingham) cardiovascular risk factors such as hypertension, left ventricular hypertrophy, hyperlipidemia, diabetes, and physical inactivity. There are several patient factors that affect survival on PD, most of which are nonmodifiable. For example, presence of diabetes, age, and ESRD etiology are all nonmodifiable independent predictors of patient survival [24].

Besides traditional cardiovascular risk factors, there are uremia-specific, nontraditional risk factors, including increased inflammation and oxidative stress, malnutrition, volume overload, anemia, and disordered mineral metabolism, all of which are associated with higher all-cause and cardiovascular mortality in dialysis patients.

In the general population, modification of traditional cardiovascular risk factors decreases morbidity and mortality. However, the benefit of modifying these traditional and also nontraditional risk factors remains unclear because randomized, placebo-controlled trials in patients with chronic kidney disease (CKD) have so far been disappointing and unable to show a survival benefit of various treatment strategies, such a lipid-lowering, increased dialysis dose and normalization of hemoglobin [25,26]. This realization has focused attention on non-traditional modifiable risk factors uniqe to the PD patients. Modifiable cardiovascular risk factors that are unique to peritoneal dialysis patients, including residual renal function, peritoneal membran integrity, infection, dialysis center size, patient education and training,

all of which are also associated with higher all-cause and cardiovascular mortality in dialysis patients.

As known that inflammation is highly prevalent in patients on dialysis and established to be a powerful predictor of mortality. Studies point to the increased concentrations of acute phase reactants and proinflammatory cytokines in chronic uremia [27-29], suggesting a chronic inflammatory state in CKD patients, especially in stages 3 to 5. Wang et al, found that in patients with high CRP levels, LVMi and left ventricular end diastolic diameter were high while ejection fraction (EF) and fractional shortening were lower. In multivariable Cox regression analysis they showed that every 1 mg/L increase in high-sensitivity C-reactive protein (hsCRP) was independently predictive of higher all-cause mortality and cardiovascular mortality in PD patients. It was also found that, other significant predictors for all-cause mortality included age, gender, atherosclerotic vascular disease, LVMi and residual GFR. In addition, age, history of heart failure, atherosclerotic vascular disease, and residual GFR were also independently predictive of cardiovascular mortality. Author concluded that, a single, random hs-CRP level has significant and independent prognostic value in PD patients [30]. Although the association between inflammation and cardiovascular diseases is well established the mechanism that inflammation accelerates this process is not clear. It was suggested that inflammation plays an important role on the development and progression of atherosclerosis through endothelial dysfunction, insulin resistance and oxidative stress such as increased lipid peroxidation and depletion of antioxidants [31].

Studies demonstrated that malnutrition prevalence is 23-76% and 18-50% respectively among hemodialysis and peritoneal dialysis patients [32-35]. Malnutrition is associated with low serum albumin, transferrin and prealbumin levels. Malnutrition indicators such as serum albumin level, subjective global assessment (SGA), daily protein-calorie intake and adjusted protein catabolism rate (nPCR) are reported to be important determinants of morbidity and mortality for PD patients in many studies [36-38]. Appetite loss because of abdominal distention in PD patients may directly causes malnutrition. It was known that chronic inflammation observed in CKD patients is an important causative factor for poor nutritional status determined in these patients. The concomitance of malnutrition and inflammation had also been indicated in the pathogenesis of increased cardiovascular morbidity and mortality in dialysis patients [39]. This situation is called the syndrome of malnutrition, inflammation, atherosclerosis (MIA) [40].

Mineral metabolism disorders, such as hyperphosphatemia is prevalent in PD patients [41]. Hyperphosphatemia has been linked to vascular and valvular calcification and there is an increasing recognition of a high prevalence of vascular and valvular calcification that may contribute to the increased cardiovascular mortality in the PD patients. Risk factors for valvular diseases or calcification are mineral metabolism disorders, dialysis duration, hypoalbuminemia, inflamation and being elderly. Valvular calcification may cause conduction disorders through regurgitation or substantial stenosis (mostly at aorta valve), hiss bundle involvement that results in complete cardiac block [42]. In a study, Wang et al demonstrated that 30% of PD patients have cardiac valve calcification [43]. The same study showed that even patients' calcium phosphorus product (CaxP) levels are normal, inflammation and malnutrition can be

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accompanied by valvular calcification. This finding proves that in addition to the association between valvular calcification and calcium phosphorus product (CaxP), inflammation and malnutrition also contribute to the process. It is known that fetuin-A is a negative acute phase protein and inhibitor of calcification. Dervisoglu et al also found negative correlation between serum fetuin-A and cytokine concentration in CKD patients [44]. This finding support the idea of inflammation-dependent down regulation of fetuin-A expression. It is reported that, serum fetuin-A independent from high serum CRP and CaxP levels is inversely related with valvular calcification [45]. This study also demonstrated that low serum fetuin-A level is associated with valvular calcification, atherosclerosis, malnutrition, and inflammation, and it is an important determinant for fatal and non-fatal cardiovascular events and all-cause mortality. Another study by Wang et al, valvular calcification was identified as a strong and independent risk factor for cardiovascular and all-cause mortality in PD patients. Clinically mortality rates similar to patients with atherosclerotic vascular complications, indicate valvular calcification to be a form of atherosclerosis [46]. Wang et al, also found an increase in the thickness of the carotid artery intima media in addition to existing valvular calcification in PD patients [47]. Malnutrition and inflammation in ESRD patients, along with high calcium load and calcium-phosphorus imbalance may also be factors that cause valvular and vascular calcification.

It is well known that anemia is also prevalent in peritoneal dialysis patients. In many studies anemia was found to be associated with high morbidity and mortality rates in peritoneal dialysis patients. Among these studies one carried out by Li et al, studied 13,974 erythropoietin-treated Medicare patients who initiated peritoneal dialysis between 1991 and 1998. Mean hemoglobin levels for the first 6 months of the study and, subsequently, time to first hospitalization and death during a 2-year follow-up were determined. They found that mortality rates in nondiabetic patients were higher in those with hemoglobin values of <10 and ≥12 g/dL. Mortality rates in diabetic patients were highest in those with hemoglobin values of <10 g/dL, followed by those with levels of 10 to 10.9 g/dL, while those in the 11 to 11.9 and ≥12 g/dL categories had similar rates. As a conclusion they stated that, anemia is associated with hospitalization and mortality in a manner supporting current Kidney Dialysis Outcomes Quality Initiative (K/DOQI) hemoglobin targets in PD patients [48].

Inflammation, malnutrition, disordered mineral metabolism, and anemia are the most common uremia-specific, nontraditional cardiovascular risk factors. They are associated with higher all-cause and cardiovascular mortality in dialysis patients. It is therefore crucial to develop effective therapeutic strategies that may prevent and potentially reverse these cardiovascular risk factors.

6. Clinical benefits of preserving residual renal function in peritoneal dialysis and the association with cardiovascular events and residual renal function in peritoneal dialysis

Observational studies showed the superiority of PD compared with HD in preserving RRF [49,50]. The rate of decline in rGFR seems to be greatest in the first 3 months of at the beginning

dialysis and falls thereafter. In a study by Jansen et al, RRF measured in ml⁄min⁄1.73 m^2 body surface area (BSA) declined from a mean of 5.8 at dialysis initiation to 2.2 after 1 year in PD patients and to 1.6 in those on HD [51].

Apart from providing small solute clearance, residual renal function contributes significantly to the overall health and well-being of patients on peritoneal dialysis. The benefits of RRF in PD extend beyond survival and there is a good evidence that it has a beneficial effect on fluid balance [52], blood pressure control [53], left ventricular hypertophy [10], hemoglobin levels [10], nutrition [54], and mineral metabolism [55].

6.1. Residual renal function, volume control, and cardiac hypertrophy

Residual renal salt and water excretion contribute substantially to the maintenance of euvolemia in PD patients with preserved RRF. It was reported that suboptimal sodium and water removal in patients on PD is associated with greater rates of all-cause hospitalization and mortality [56]. In the CANUSA study, urine volume was also a powerful predictor of survival. Every 250-mL/day urine output was associated with a 36% decrease in the RR of death [5]. In a prospective study it was performed in 25 of 37 PD patients and extracellular water (ECW) (by using sodium bromide); total body water (TBW) (by using deuterium oxide), peritoneal transport characteristics (D/P creat. ratio), rGFR (by urine collection) and CRP were assessed. It was found that rGFR was associated with lower extracellular fluid (ECF) volume [57]. In another retrospective study it was performed in 600 PD patients and PD adequacy, transport status, and multifrequency bioimpedance measurements of extracellular water to total body water (ECW/TBW) were evaluated. It was found that on their multivariate analysis %ECW/TBW was associated with age, number of antihypertensive medications, log CRP, and negatively with serum albumin and RRF. Authors concluded that overhydration as assessed by ECW/TBW is prevalent in PD patients, and is associated with loss of residual renal function, inflammation, malnutrition and hypertension [52].

Preservation of RRF may reduce or obviate the need for fluid restriction. RRF is also likely to decrease the need for volume removal with dialysis, and to help prevent the need for high glucose exchanges. With declining RRF, sodium and water removal become inadequate, leading to more volume overload and worsening of arterial hypertension [52,58], which is associated with more severe LVH [59].

A study demonstrated that arterial pulse pressure is the most significant blood pressure parameter in predicting future LVMi and change in LVMi in the general population [60]. This observation also confirmed in dialysis patients. In a study it was reported that arterial pulse pressure was independently associated with LVH in dialysis patients. Moreover, arterial pulse pressure was significantly and positively correlated with rGFR in PD patients in this study [10].

Wang et al, was also demonstrated an important association between degree of RRF and severity of LVH in PD patients. Moreover, loss of RRF is also associated with more severe anemia, greater degree of hypoalbuminemia, and higher arterial pressure, all of which are important risk factors for cardiac hypertrophy in patients on dialysis [10]. However, the association between LVH and RRF could not be fully explained by anemia, hypoalbuminemia,

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hypervolemia or hypertension. It was showed that in pre-dialysis patients, the decline in renal function was associated with an increase in the LVH [61]. After a successful kidney transplantation Riggato et al, demonstrated a regression in LVH [62]. Both of these observations suggest that degree of uremia and loss of RRF may be important in determining the LVH. The link between loss of residual renal function and cardiac hypertrophy may also explain that some non-dialyzable uremic toxins may be important in the progression of left ventricular hypertrophy in peritoneal dialysis patients and needs further evaluation.

6.2. Residual renal function and metabolic control

RRF plays an important role for removal of middle molecules and protein-bound solutes which are increasingly recognized as important uremic toxins. Cross-sectional and prospective studies by Bammens et al [63], and Pham et al [64], showed that the contribution of renal to total clearance of middle molecules (β2-microglobulin) and proteinbound substances (*P*-cresol, *P*-cresol sulfate, indican) was much greater than the renal contribution to total small-solute clearance. Patients with significant RRF are shown to have lower β2-microglobulin levels [65], and are thus, less prone to dialysis-associated amyloidosis [66], Bammens et al [63], also showed that with a progressive decrease in RRF, increasing the PD dose was able to compensate for loss of renal clearances of such small water-soluble solutes as urea and creatinine. However, permanent irreversible decreases were seen in the total clearance of middle molecules and protein-bound substances.

In PD patients it was found that RRF is positively and directly related to hemoglobin levels and nutrition parameters such as serum albumin and nPCR [67]. In 158 non-diabetic PD patients, Wang et al. showed that patients with better residual GFR were less anemic and had lower degree of hypoalbuminemia. Human erythropoietin levels were found higher in patients with RRF on maintenance hemodialysis and positively correlated with rGFR [68]. This finding shows that presence of RRF even in a small amount, account for considerable improvements in the degree of anemia.

Hyperphosphatemia is a common problem encountered in PD and HD patients and has been linked to vascular calcification and increased cardiovascular mortality in these patients [41,69]. A study was performed by Wang et al, in 252 prevalent Chinese PD patients. They found that, serum phosphorus levels were 5.6 mg/dL or greater in 44.0% of anuric patients versus 28.7% of patients with RRF. Their multiple regression analysis showed that residual glomerular filtration, despite an average of less than 2 mL/min/1.73 m^2, was independently associated with phosphorus control in PD patients. In this study was also showed that, residual GFR was negatively correlated with serum phosphorus and the product of calcium with phosphorus levels, indicating the contribution of the presence of RRF to the phosphate balance in such patients [70]. Dervisoglu et al, was also showed that residual GFR was associated with phosphorus control [71]. As a conclusion, after ingestion of dietary phosphorus, RRF is the most important factor in the control of serum phosphorus level in PD patients.

6.3. Residual renal function and inflammation and nutritional status

As mentioned above, inflammation and malnutrition are highly prevalent among dialysis patients and they are associated with higher all-cause and cardiovascular mortality in dialysis patients. Loss of RRF is also associated with increased inflammation and malnutrition in PD patients.

Chung et al, performed a retrospective analysis in new 117 peritoneal dialysis patients with initial assessments for RRF and serum CRP. It was found that patients with low RRF were older and had a higher prevalence of high CRP. In their multiple regression analysis, age and RRF were identified as factors affecting inflammation. Overall patient survival was significantly lower in the patients with low RRF, with high CRP. Authors concluded that these results indicate that in patients starting PD, low initial RRF is associated with inflammation, and low RRF and inflammation are both associated with high overall mortality [72]. In a prospective observational study, it was conducted a cohort of 160 PD patients with a mean follow-up of 35 +/- 16 (SD) months. At baseline, echocardiography and standard clinical and biochemical analyses and markers of inflammation such as circulating soluble vascular cell adhesion molecule 1(sVCAM-1) and CRP were performed in all patients. Serum sVCAM-1 levels were elevated in PD patients and showed a negative correlation with rGFR but a positive correlation with LVMi. Furthermore, patients with both sVCAM-1 and CRP levels elevated at the 50th percentile or greater were associated with the greatest death and fatal and nonfatal cardiovascular event rates [73]. In similar, using high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), as markers of inflammation a study indicated that a low GFR is also associated with an higher inflammatory state [74].

Conversely, inflammation may exert negative effects on RRF. For example, in a retrospective analysis it was performed in 80 patients to identify risk factors influencing the decline of RRF after the initiation of peritoneal dialysis. It was found that the only independent risk factor for the decline of RRF was the rate of peritonitis by linear multiple regression analysis. This observation suggest that the presence of inflammation may accelerate the decline of RRF [75]. The exact mechanism of the relationship between residual renal function and inflammation are not clear. Although, more inflammation may have had a greater tendency to a decrease in RRF, it also is possible that loss of RRF may enhance inflammatory response and impaire cytokine clearance.

The impact of RRF on nutritional status in dialysis patients has also studied in some studies. Markers of nutritional status, such as subjective global assessment, lean body mass, and handgrip strength, all correlate with RRF in PD patients. Wang et al, performed a cross-sectional study on 242 PD patients. Appetite, dietary protein, and total calorie intake assessed by using food questionnaires appear to be enhanced in the presence of RRF. Authors was concluded that this study confirmed significant and independent effect of RRF, on dietary intake, and other nutrient intake in PD patients [76]. These may relate to the enhanced renal elimination of appetite-suppressing cytokines and liberalization of diet in the face of preserved RRF also may explain the increases in dietary intake. Another prospective observational study was conducted a cohort of 251 PD patients with a mean follow-up of 28.7 ± 14.3 months. Resting energy expenditure (REE) was measured at study baseline using indirect calorimetry together

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with other clinical, nutritional, and dialysis parameters. Anuric PD patients have been shown to have greater resting energy expenditure compared with patients with RRF. Using multiple regression analysis, adjusted REE was negatively associated with rGFR and serum albumin and positively associated with diabetes, cardiovascular disease, and CRP. At 2 year, the overall survival was 63.3, 73.6, and 95.9%, and cardiovascular event-free survival was 72.3, 84.6, and 97.2%, respectively, for patients in the upper, middle, and lower tertiles of REE. The significance of REE in predicting mortality was gradually reduced when additional adjustment was made for CRP, serum albumin, and rGFR in a stepwise manner. Author concluded that a higher REE is associated with increased mortality and cardiovascular death in PD patients and is partly related to its close correlations with residual kidney function, cardiovascular disease, inflammation, and malnutrition in these patients [77]. In patients on PD, it was also shown that patients without RRF had lower nPCR and serum albumin levels than their total weekly clearance (Kt/V) equal counterparts [78]. In another cross- sectional and multicenteric study, it was shown that the loss of renal function is associated with anorexia and symptoms of severe malnutrition in PD patients [79]. In a study it was also found that RRF was positively correlated with nutrition markers and negatively correlated with CRP. Moreover, as compared with patients without inflammation, patients with inflammation had significantly lower hemoglobin, serum prealbumin levels, and serum transferrin levels and a higher erythropoietin resistance index [54].

In summary, these findings suggested that loss of residual renal function contributes significantly to inflammation and malnutrition in peritoneal dialysis patients.

As mentioned above, LVH starts in early CKD, is present in 75% of patients entering dialysis, and is progressive thereafter. LVH is perhaps the most powerful indicator of cardiovascular events and mortality in patients with dialysis patients. Studies reported that the presence and progression of LVH was strongly linked to subsequent cardiovascular events and mortality in dialysis patients [11,21].

In 2002, Wang et al, were among the first to note an inversely relationship between the presence of RRF and LVH. A cross-sectional study was performed with LVMi, determined in 158 non-diabetic PD patients using echocardiography and its relationship with rGFR, and other known risk factors for LVH was evaluated. Only 12 patients had no LVH. The remaining 146 patients were stratified three groups according to the LVMi. Across the four groups of patients with increasing LVMi, there was significant decline in RRF. Patients with better-preserved RRF were less anemic and hypoalbuminemic and had a trend toward lower systolic blood pressure and arterial pulse pressure. Multiple regression analysis showed that other than age, gender, body weight, arterial pulse pressure, hemoglobin and serum albumin, known factors for LVH, RRF was also independently associated with LVMi [10]. In a recent prospective observational study with 2 years of follow-up, it was conducted a cohort of 156 PD patients with a mean follow-up of 19.2 ± 6.4 months. At baseline, echocardiography and standard clinical and biochemical analyses were performed in all patients and in 28 healthy subjects. During the follow-up period, 25 of the patients (16.0%) died, and 10 of those deaths had CV causes. Nonfatal CV events occurred in 15 patients. In the fully adjusted multivariate Cox regression analysis (co-variates: age, sex, albumin, hemoglobin, diabetes mellitus, comorbid CVD, LVMi,

rGFR, dialysate-to-plasma ratio of creatinine, Kt/V urea, left ventricular ejection fraction, duration of dialysis, smoking), aortic stiffness index beta independently predicted fatal and nonfatal CV events, but not all-cause mortality. Moreover, all-cause mortality was predicted by age, serum albumin, and LVMi. Increases in age and in LVMi increased the risk of all-case mortality, but increases in serum albumin reduced that risk [80].

Wang et al, also performed a prospective study in 240 PD (39% being completely anuric) patients. It was found that the overall 2 year patient survival was 89.7 and 65.0 % for patients with preserved RRF and anuric patients, respectively. Compared with patients with preserved RRF, anuric patients were dialysed for longer, were more anaemic, and had higher calcium-phosphorus product, higher CRP, lower serum albumin, greater prevalence of malnutrition and more severe cardiac hypertrophy at baseline. Using multivariable Cox regression analysis, serum albumin, left ventricular mass index and residual GFR were significant factors associated with mortality in patients with RRF, while increasing age, atherosclerotic vascular disease and higher CRP were associated with greater mortality in anuric PD patients [55].

In another prospective observational study it was performed in 231 PD patients and LVMi, rGFR, CRP, hemoglobin, and serum albumin were determined at study baseline and related to outcomes. After follow-up for 30±14 month, 34.2% patients had died. CRP, RRF, and LVMi each were significantly predictive of all-cause mortality and cardiovascular death. Authors concluded that inflammation, RRF, and LVH are interrelated and combine adversely to increase mortality and cardiovascular death risk of PD patients [81].

Szeto et al, also performed a retrospective review to study the cause of death of 296 PD patients over a 7 year period, and compared the mortality and distribution of cause of death between patients with and without residual renal function. As expected, they found that, there was a higher proportion of vascular deaths in patients with pre-existing cardiovascular disease than those without (61.5 vs 40.6%). In addition, when patients with and without pre-existing cardiovascular disease were analysed separately, patients without pre-existing cardiovascular disease more commonly died of vascular disease after they become anuric (47.4 vs 34%). More importantly, for patients with pre-existing cardiovascular disease, there was no significant difference in the distribution of cause of death between those with and without RRF. As a result, they stated that, anuric patients had a higher mortality (nearly 50%) than those with preserved residual renal function, vascular disease was a more common cause of death in anuric patients than those with RRF (55.3 vs 40.8%). The difference was largely explained by the higher prevalence of sudden cardiac death in anuric patients (39 in 149 cases vs 19 in 147 cases) [82].

Ateş et al, performed a prospective study in 125 PD patients. Patients were monitored for three years from the beginning of the treatment. The effects of comorbidity, blood pressure, blood biochemistry, peritoneal membrane transport characteristics, Kt/V(urea), total creatinine clearance (TCC), RRF, and removal of sodium and fluid on mortality were evaluated. It was found that comorbidity, hypertensive status, serum creatinine, and total sodium and fluid removals were independent factors affecting survival in the Cox model. It was also demonstrated that RRF has a major impact on patient survival. It was also reported that Kt/V(urea) or TCC did not affect the adjusted survivals. Authors concluded that adequate fluid and

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sodium balance is crucial for the management of patients on PD. It was also suggested that RRF may have an important impact on the ability to maintain sodium and fluid balance in PD patients [56].

Both of these observations suggest that loss of RRF may be important in determining the LVH and subsequent cardiovascular events and mortality in dialysis patients.

7. Preservation of residual renal function

Both volume expansion and the high urea load per nephron are rapidly reversed by dialysis of any form. Therefore, many patients have a marked reduction in, or even cessation of, urine output when dialysis is instituted [83]. Peritoneal dialysis and hemodialysis may have different effects on residual renal function. As mentioned above, RRF is preserved longer in peritoneal dialysis than hemodialysis patients, but data from prospective randomized trials are lacking [49,50]. Potential reasons for RRF preservation in PD are related to better hemodynamic stability with PD that may minimize ischemic renal insults and avoidance of the extracorporeal circulation of HD that activates nephrotoxic inflammatory mediators during treatments and subsequent kidney injury [51,84,85]. However the use of ultrapure water and biocompatible membranes during HD have been shown to slow the loss of RRF in incident patients on HD [86,87]. Use of PD as an initial dialysis modality in patients with RRF has been suggested as strategy to maximize RRF preservation and, thus, survival for patients on dialysis.

Some studies suggested that automated forms of peritoneal dialysis (APD) might be associated with a more rapid decline in residual renal function and was hypothesized to be related to less stable fluid and osmotic load together with intermittent nature of APD. Other studies have found minimal effect of PD modality on the loss of residual renal function [88-91].

The newer biocompatible peritoneal dialysis solutions may slow the decline in RRF in peritoneal dialysis patients. In a multicenter, open, randomized, prospective study with a crossover design and parallel arms, a conventional, acidic, lactate-buffered fluid was compared with a pH neutral, lactate-buffered, low glucose degradation products (GDP) fluid (balance). It was concluded that the balance solution, a neutral pH, low GDP fluid, results in an improvement in local peritoneal homeostasis, as well as having a positive impact on systemic parameters, including circulating advanced glycosylation end products (AGE) and RRF [92]. In another randomized controlled study was conducted comparing use of biocompatible with standard solutions in 93 incident PD patients during a 1-year period. At 3 and 12 months, 24-hour urine samples were collected to measure volume and the mean of urea and creatinine clearance normalized to body surface area. It was demonstrated that changes in the normalized mean urea and creatinine clearance were the same for both groups, with no significant differences in secondary end points. Author concluded that the newer biocompatible solutions have not any clinically significant advantages [93]. Similarly, apparently conflicting results are present with the use of icodextrin in PD [94-96].

Loop diuretics appear beneficial in increasing urine and sodium excretion and improve fluid balance in dialysis patients with RRF, but there is so far no evidence that it preserves residual

renal function. It was found that, the use of furosemide in a randomized trial of patients on PD, has no significant detrimental or beneficial effect on RRF [97]. Diuretics are likely to decrease the need for volume removal with dialysis, and to help prevent the need for high glucose exchanges.

Blockade of the renin–angiotensin system by angiotensin-converting enzyme inhibition or angiotensin receptor antagonism is a well-known approach for nephroprotection in pre-dialysis chronic kidney disease patients. The angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may also slow the decline in residual renal function in peritoneal dialysis patients. Li et al, was performed a study in 60 peritoneal dialysis patients who were randomly assigned to ramipril (5 mg/day) or no treatment. It was found that the average rGFR at one year was significantly higher among those given ramipril (1.72 and 0.64 mL/min per 1.73 m^2) [98]. Similar benefits in terms of preserving residual renal function have been observed with an angiotensin II receptor blocker. Suzuki et al, was also performed a randomized two-year controlled study in 34 peritoneal dialysis patients [99]. It was observed that valsartan maintained residual renal function (3.2 mL/min per 1.73 m^2 at baseline to 4.3 mL/min per 1.73 m^2) and total clearance (42.1 to 48.3 L/week per 1.73 m^2); compared with the control group, residual renal function decreased (5.9 to 2.8 mL/min per 1.73 m^2) and total clearance declined (47.1 to 31.4 L/week per 1.73 m^2). Significant differences between the two groups in terms of RRF were noted at two-year study end. These findings led the 2006 K/DOQI work group for peritoneal dialysis adequacy to recommend the use of ACE inhibitors and/or ARBs for the treatment of hypertension in patients who have RRF, because these agents may help decrease the decline in residual renal function [13]. They suggest that such agents should also be considered for nephroprotection among normotensive peritoneal dialysis patients. However, at present, there is not enough evidence to recommend the use of these agents in normotensive patients, unless they have other specific indications for these medications (such as heart failure).

The most importance strategy for preservation of RRF is avoidance of hypovolemia in peritoneal dialysis patients. Data from Netherlands Cooperative Study on the Adequacy of Dialysis study suggest that episodes hypovolemia were an independent risk factor for the loss of RRF in peritoneal dialysis patients [6]. But some authors believed that there is a cause-effect relationship between volume overload and preserving RRF in peritoneal dialysis patients. For example, Gunal et al, applied strict volume control with strong dietary salt restriction alone or combined with increased ultrafiltration (UF) in 47 peritoneal dialysis patients. Cardiothoracic index (CTI) on the chest radiograph was used as a measure of volume control. It was demonstrated that CTI decreased from 48.0% +/- 5.6% to 42.9% +/- 4.5% in 37 patients. In 19 patients who had residual renal function, 24-hour urine volume decreased to 28% of the pretreatment volume, accompanied by a mean decrease in Kt/V urea from 2.06 +/- 0.5 to 1.85 +/- 0.4 [100].

Aminoglycosides have been proven to be an efficacious treatment for peritonitis in peritoneal dialysis patients for many years. However, with the increasing emphasis on preserving residual renal function, there has been concern about the nephrotoxic potential of these compounds. However, some studies have found no effect of aminoglycoside use on the decline

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of RRF. In a study, preperitonitis and postperitonitis RRF were determined for 70 peritonitis episodes treated with the aminoglycoside-based regimen, 61 episodes treated without aminoglycosides, and 74 control patients without peritonitis. There was no evidence of an accelerated decline in RRF when using an empirical regimen containing aminoglycosides for peritonitis [101]. In another retrospective study it was also demonstrated that the change in residual renal function over time was similar in 1075 patients who treated with the aminoglycoside-based regimen for peritonitis as compared with 339 who did not [102].

In similar, with the increasing emphasis on preserving residual renal function, there has also been concern about the nephrotoxic potential of iodinated radiocontrast agents. In one prospective study, the RRF was evaluated at baseline and two weeks after contrast administration in 36 peritoneal dialysis patients and 36 control patients also underwent determination of RRF two weeks apart. In the contrast group, the study was performed with adequate prehydration and a minimum dose of contrast medium. Compared with baseline values, RRF and daily urine volume were not found to be significantly different 2 weeks after contrast. Following contrast, variations in RRF and daily urine volume were found to be comparable with those of the control group [103]. In a study of 10 peritoneal dialysis patients who received non-ionic hypo-osmolar contrast media, RRF (calculated as the average of renal creatinine and renal urea clearance) was measured on the day before the intervention (baseline), on days 1-7, day 10 and day 30 after intervention. It was observed a temporary decline of residual renal function after administration of contrast media, but on day 30, residual renal function were not significantly different from baseline [104]. But authors concluded that, non-ionic hypo-osmolar contrast media should be given to PD patients with the lowest possible dose and only if there is a real clinical indication.

In summary, strategies for preservation of RRF are avoidance of hypovolemia, avoidance of nephrotoxic drugs and agents (such as radiocontrast agents, nonsteroidal antiinflammatory drugs or aminoglycosides), the use of high dose of loop diuretics and the use of an ACE inhibitors or ARBs.

8. Conclusion

Residual renal function contributes significantly to the overall health and well-being of patients on PD. RRF has been implicated to be important in maintaining the fluid balance of patients on PD. RRF also plays an important role in phosphorus control, and removal of middle molecular uremic toxins. In addition, loss of RRF is associated with higher arterial pressure, more severe anemia, greater degree of inflammation and malnutrition. More importantly, loss of residual renal function is associated with greater degree LVH and more subsequent cardiovascular events and higher mortality in peritoneal dialysis patients. The contribution of residual renal and peritoneal dialysis clearance to the survival of peritoneal dialysis patients is not equivalent. Furthermore the loss of RRF may not be simply replaced by increasing peritoneal dialysis dose. It is therefore crucial to develop effective therapeutic strategies that may preserve RRF in peritoneal dialysis patients.

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