Remnant Proteinuria in Chronic Hemodialysis

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Additional information is available at the end of the chapter

1. Introduction

Patients with end-stage renal disease are at high risk of developing cardiovascular disease. In addition to the major traditional risk factors for cardiovascular disease (ie, advanced age, hypertension, diabetes mellitus, dyslipidemia, and smoking), recent studies suggest that chronic kidney disease is an independent risk factor [1] Several groups have reported that coronary artery disease severity and lesion complexity are associated with a decrease in the estimated glomerular filtration rate [2,3] Recent epidemiological studies and clinical trials have demonstrated that chronic kidney disease is associated with increased mortality rate in patients with cardiovascular disease [4,5]. Notwithstanding the deep deleterious effects chronic renal disease itself plays in endothelial and medial arterial wall, renal failure leads to both significant increases in morbidity and decreases in life survival, particularly in hemodialysis patients, who represent the most severe and advanced expression of renal disease.

The mechanisms that underlie the association between renal dysfunction and coronary artery disease have not been elucidated fully. Previous studies have shown that renal dysfunction is associated with low-grade inflammation and activation of the sympathetic nervous system and of the renin-angiotensin aldosterone system [6-8]. Other factors such as calcium-phosphate disbalance, oxidative stress, hyperglycemia, advanced glycosylated end-products, and abnormal apolipoprotein levels also were shown, among others, to promote renal dysfunction [9,10]. As such, these factors could also contribute to the pathogenesis of atherosclerosis.

As renal function deteriorates at early stages, the different organ systems start to experience subtle alterations. These initial disturbances that develop at the molecular level, encompass mainly chronic inflammatory pathways mediated by cytokines secreted by leukocytes and uremic retention toxins. In turn, and with different degrees of clinical and biochemical mani-

festations, the many culprits interact and cause systemic impacts. The most important, albeit not the one, harmful effect is evident at the cardiovascular level. This is due to the fact that the endothelium is a direct target of plasmatic toxins, free radicals and altered synthesized molecules, abnormal platelets, short-live erythrocytes and malfunctioning leukocytes, hyperglycemia, dyslipidemia and hypertension. The damaged endothelium interacts with both the plasmatic and cellular constituents of blood and the inner vessel wall cells, particularly smooth muscle cells, circulating monocytes and tissular macrophages and fibroblasts. The direct consequences are vascular thrombosis, calcification and lipid deposition, and tissue hypoxia. Although these mentioned vascular alterations exist in all organ systems, the central nervous system, the heart and the kidneys are the most important clinically involved organs. This situation finds its most critical exponent when kidney function reaches stage 5 and uremia is present [11]. At this stage, renal replacement therapy is mandatory. Among the therapeutic options, hemodialysis, peritoneal dialysis and kidney transplantation are available. These options are far from ideal, albeit transplantation offers the best results. With respect to the dialysis procedures, hemodialysis is the most frequent modality employed worldwide to treat end-stage renal disease. Among the factors that add morbidity and mortality to hemodialysis individuals are -as mentioned- comorbid conditions as diabetes mellitus, hypertension, aging, endocrine and electrolyte derangements, oxidative stress, volume overload, hyporexia and nutrient losses during the dialysis process, dialysis devices and vascular access-blood interactions, the predisposition to infections, and water quality. All these main factors will definitively result in a vicious cycle in which protein energy wasting, malnutrition, uremic toxins retention, inflammation, and a hypercatabolic state with grim and most frequently irreversible consequences harmfully interact. Cardiovascular disease, malnourishment and inflammation are the main roads that can merge or independently lead to premature death, the reality dialysis patients still face nowadays [11,12].

As mentioned before, many clinical, nutritional, and biochemical parameters may be indicating a chronic inflammatory state in these individuals. Conventional and non-traditional risk factors and metabolic alterations observed in the uremic milieu may contribute to the excessive risk of cardiovascular disease [12]. Both Framingham and the so called *non-traditional* risk factors as inflammation, endothelial dysfunction, sympathetic activation, protein-energy wasting, oxidative stress, vascular calcification, and volume overload may play relevant roles in the development of vascular disease in dialysis patients [13-15]. However, it has recently demonstrated that the addition of multimarker scores (including markers of inflammation and volume overload) to conventional risk factors resulted only in small increases in the ability to grade risk, at least in the general population [16,17].

An important factor in hemodialysis that is linked to survival is residual renal function, clinically assessed as the amount of daily urinary output. Many factors conspire against this important variable: Lifetime on dialysis, aging, the etiologies of end-stage renal disease and higher degrees of ultrafiltration. However, proteinuria, an important marker of progression of renal disease that is associated in time with decreased renal function and oliguria, is not assessed routinely in hemodialysis.

The aim of the present chapter is to consider remnant proteinuria as an active marker of inflammation and cardiovascular disease, and also as a cause of decrease of residual renal function and urinary output in hemodialysis. Although not yet assessed, it is reasonable to presume that also in hemodialysis patients, proteinuria should be associated with increased cardiovascular events, inflammatory processes and decreased life survival.

2. Residual renal function in dialysis

In recent years, there has been a greater focus on residual renal function of patients on chronic dialysis therapy. Although residual renal function is often used to indicate remaining glomerular filtration rate, it also reflects remaining endocrine functions such as erythropoietin production [18], calcium, phosphorus and vitamin D homeostasis [19,20], volume control, and removal of "middle molecules" or low molecular weight proteins [21,22]. It is assumed by some authors that an estimated urine volume < 200 ml/24 h should be considered as a cut-off to consider loss of residual renal function. However, several of the significant associations with residual renal function loss have generated testable hypotheses regarding potential therapies that may preserve renal function among dialysis patients that may be independent of the urinary volume, even at less than 200 ml daily. Renal replacement function is clinically important in that it can account for major differences in dialysis requirements, since it contributes to measures of adequacy, both Kt/V urea and creatinine clearance [23,24]. As mentioned before, residual renal function has also been shown to be associated with mortality. Analysis of the CANUSA study [25] has shown that every 0.5 ml/min higher glomerular filtration rate was associated with a 9% lower risk of death in subjects with renal disease but not still in dialysis [26]. It has been shown that clinically important and statistically significant decreases in nutritional parameters occur with residual renal function loss [25]. Furthermore, it has been demonstrated that small increments in it may account for major differences in quality of life [27,28]. It is therefore very important to determine and understand the predictors of loss of residual renal function in the dialysis patient. The importance of identifying factors that protect and preserve renal function has been recognized among patients with chronic renal failure and pre-end-stage renal disease (stages 3 and 4). Control of blood pressure, angiotensin-converting enzyme inhibition, decreasing proteinuria, dietary modification, avoidance of nephrotoxins, and glucose control have all been considered integral parts of the pre-stage 5 care [29]. However, few studies have comprehensively evaluated whether these or other factors are important in preserving residual renal function after initiation of dialysis. Also on a clinical level, evaluating and monitoring factors that preserve it in patients who have just started dialysis has not received the same level of care as among the chronic renal failure population. It is also probable that subjects with stage 5D (under dialysis) may be treated differently than stage 5 subjects not still in dialysis: In stage 5 not in dialysis, individuals may be under pharmacologic regimes to control proteinuria, that may be left aside when dialysis is started, or the beneficial effects of which are not carefully assessed or even considered.

Several authors have observed that preservation of residual renal function is prolonged with peritoneal dialysis compared to hemodialysis [30-32]. Others have noted a more rapid decline in renal function among patients on automated peritoneal dialysis versus continuous ambulatory peritoneal dialysis [33]. For hemodialysis patients, there has been debate in the literature about whether the type of dialyzer membrane has an effect on remnant renal function. Some have suggested that biocompatible membranes preserve renal function for a longer time period [34-36]. Cause of end-stage renal disease, level of blood pressure, rate and profile of fluid removal, contrast materials as iodide and gadolinium, and also various medications have all been implicated as having an effect on renal function [29,37,38]. However, the current knowledge about the factors that preserve renal function in end-stage renal disease is still very limited. Daily urinary volume recollection may be cumbersome and imprecise, but has proved to be a useful measure of residual renal function. It is interesting that patients are more likely to have the outcome variable, urine volume, reported if they are on peritoneal dialysis or if they are female. It has been recognized that residual renal function is important in continous ambulatory peritoneal dialysis due to its contribution to small solute clearance, and more attention may be paid to monitoring it in this population. The reason for the gender difference is not clear. Several studies about the progression of chronic renal disease have reported that the decline in renal function is either linear or exponential [29,39]. Thus, it is assumed that longer follow- up and lower levels of renal function at the start of dialysis would be associated with a greater likelihood of loss of residual renal function. It is therefore necessary to control for these factors when evaluating the effect of other potential predictors. Duration of time on dialysis is indeed a significant predictor of renal function loss in the overall population and among the peritoneal dialysis population, but, interestingly, not among the hemodialysis population. Among the peritoneal dialysis patients, there is an increasing risk of loss of residual renal function over time, suggesting that time on dialysis is an important variable. Likewise, higher estimated glomerular filtration rates at dialysis initiation is associated with lower risk of loss of residual renal function at follow-up among peritoneal dialysis-treated patients but not among hemodialysis-treated patients.

Increasing age may not be associated with residual renal function loss. This is consistent with data from the Modification of Diet in Renal Disease (MDRD) study [29], in which age was not an independent predictor of progression of renal disease among patients with chronic renal failure. Female gender independently predicted renal function loss loss in the overall analysis and in the analysis limited to peritoneal dialysis patients. This gender effect could not be explained by differences in body mass index, mean arterial pressure, albumin, estrogen use, or menopausal status because the effect remained despite controlling for these variables [40]. However, other studies have shown the opposite, in which a slower rate of progression of renal function decline was reported in females with chronic renal failure [41-44]. Data from the MDRD study indicated a slower mean glomerular filtration rate decline in women compared to men with chronic renal failure. However, gender differences were reduced and no longer significant after controlling for baseline proteinuria, mean arterial pressure, and HDL cholesterol [29]. Non-white race was associated with residual renal function loss in the overall analysis; however, this effect was found to be limited to peritoneal dialysis patients only. This was true of both blacks and the category "other non-white

race." These relationships were independent of cause of renal disease and blood pressure at dialysis initiation, and also could not be explained by reported differences in pre-dialysis care. African-Americans are known to have a faster rate of progression of renal failure in the chronic renal failure population [29,45]. This analysis suggests that, at least among perito‐ neal dialysis-treated patients, this race effect may persist after dialysis initiation. The pres‐ ence of diabetes predicts renal function loss particularly in both dialysis populations. Diabetic patients with hypertension and proteinuria have been shown to have an increased rate of loss of renal function in the chronic renal failure community. A history of congestive heart failure may also predict renal function loss, likely due to decreased blood flow to the compromised kidney. However, this statement has not been assessed properly in hemodial‐ ysis patients.

Several comparative studies of peritoneal dialysis and hemodialysis mortality have shown that the relative mortality risk favors peritoneal dialysis to the greatest degree early after end-stage renal disease start and the relative mortality risk increases for peritoneal dialysis with time on dialysis [46-49]. One reason that peritoneal dialysis may offer this early advant‐ age may be the greater preservation of residual renal function. Higher postdialysis blood pressure at baseline appears to correlate with a lower risk of renal function loss loss in the hemodialysis-only population but may be an insignificant predictor in the peritoneal dialy‐ sis subjects. Several studies have observed a relationship of higher mortality associated with low predialysis blood pressure [50-52]. A similar phenomenon may exist for residual renal function. Previous studies have shown that use of cellulose dialyzer membranes among he‐ modialysis patients hastens residual renal function loss [34,36] due to blood and cellulose dialysis membrane interactions, which may induce potentially nephrotoxic inflammatory mediators [53].

Comparing peritoneal dialysis patients to hemodialysis patients using biocompatible mem‐ branes revealed that peritoneal dialysis patients are still significantly less likely to lose resid‐ ual renal function than hemodialysis patients. Preservation of residual renal function is an important goal. In addition to identifying demographic groups at risk, it is also important to identify other potentially modifiable factors as calcium and phosphorus metabolism, blood pressure, hyperglycemia, PTH and vitamin D levels, dose of erythropoietin, use of iron, and therapies (dialysis modality, angiotensin converting enzyme inhibitors or angiotensin recep‐ tor blockers, calcium channel blockers, statins and aspirin) that are involved in residual re‐ nal function. There appear to be substantial differences in both the actual loss of residual renal function and the contributing risk factors among peritoneal dialysis compared to he‐ modialysis patients. Additional prospective studies, ideally clinical trials, are necessary to determine whether these possible interventions are efficacious. Proteinuria has not been as‐ sessed in any of both modalities as a marker of progression of residual renal function loss, and as a cause of cardiovascular disease and inflammation [40].

In peritoneal dialysis, the best means for assessing adequacy remain ill defined [54]. The concept of adequate dialysis should include some defined level of solute removal, adequate fluid removal to achieve normal volume homeostasis and blood pressure control, mainte‐ nance of adequate nutrition, normal acid–base balance, normal mineral metabolism, mini-

mal anemia, normal lipid metabolism, and prevention of atherosclerosis. Small solute clearance has traditionally been an integral part of the overall definition of peritoneal dialysis adequacy; most other measures appear to parallel solute removal. The importance of small solute clearance in peritoneal dialysis has been confirmed by a variety of studies [55,56], most notably CANUSA, which showed that Kt/V and corrected creatinine clearance independently predict patient survival. All these studies have been confounded by residual renal function. Solute removal by peritoneal dialysis may not be clinically equivalent to an equal quantitated solute removal by residual renal function. For example, the increased fractional secretion of creatinine during declining glomerular filtration rate can be extremely misleading if other solutes do not show a fractional increase in excretion. Conversely, the increased secretion of organic solutes during chronic renal failure may far exceed the diffusive losses of the same solute during peritoneal dialysis. Hence, the relative effects of renal versus peritoneal clearance on survival remain to be elucidated. There is consensus that residual renal function has a major impact on the ability to achieve small solute clearance targets [57]. Residual renal function contributes to approximately 25% of total Kt/V and 40% of total weekly creatinine clearance. This numerical contribution is even greater for high and middle molecular weight solutes. As residual renal function deteriorates, failure to compensate for this loss will result in an increasing frequency of inadequate dialysis. Even with increasing dialysis prescription, as many as 40% of continuous ambulatory peritoneal dialysis patients fail to meet the target [58,59]. Small changes in residual renal function with time on peritoneal dialysis may account for major differences in quality of life and dialysis outcome. Data from the CANUSA study showed that the overall outcome was worse for patients who lost their residual renal function [60,61]. The adverse impact of loss of residual renal function on outcome in peritoneal dialysis patients could be due partly to loss of residual diuresis and difficulty in managing fluid status, hypertension, and left ventricular hypertrophy, all of which contribute to cardiovascular mortality [62].

Residual renal function has also been shown to have a greater influence on dietary protein intake and nutritional status than peritoneal clearance [63-65]. Following the initial observation of Rottembourg et al., a number of studies have shown that the decline in residual renal function is more protracted in patients on peritoneal dialysis than those on hemodialysis [31,66-69]. However, the changes in residual renal function with time are not uniform in all patients. The issue of which factors affect preservation of residual renal function in patients with chronic renal failure once dialysis is started has received very little attention [70-74]. There appears to be a gradual deterioration of residual glomerular filtration rate with time on peritoneal dilaysis, with 33% of patients developing anuria at a mean of 20 months after the start of dialysis, according to Singal et al data [75]. In that study, on comparison between patients in the highest and lowest quartiles of slope for residual glomerular filtration rate, male gender, presence of diabetes, higher grades of left ventricular dysfunction, and glomerular filtration rate higher 24-hour urine protein excretion corresponded with faster decline of residual renal function. Singal et al could not show a good correlation between the decline of urine volume and renal glomerular filtration rate. Urine volume was well maintained until 30 months after start of peritoneal dialysis. This was in contrast to previous studies, where the decline in creatinine clearance and urine volume in individual patients

was significantly correlated [76]. A number of studies have shown that residual renal function is better preserved in peritoneal dialysis patients than in those on hemodialysis. However, all these comparisons were made between hemodialysis using conventional bioincompatible membranes and peritoneal dialysis. The advent of newer dialytic techniques such as automated peritoneal dialysis and biocompatible hemodialysis membranes may alter this relationship. It has also been suggested that peritoneal dialysis patients with rapidly falling residual renal function depart from therapy at a high rate, leaving those with better preservation of residual renal function on peritoneal dialysis after many months [77]. Previous studies have not clearly defined the factors that affect the rate of residual renal function loss in patients on dialysis. In hemodialysis patients, Iest et al. reported that the mean rate of decline of residual renal function was unaffected by weight, gender, age, hypertension status or medications, and by the original disease [78]. Lutes et al. also reported in 32 peritoneal dialysis patients no influence of age, diabetes, mean arterial pressure, peritonitis rate, and initial creatinine clearance at the start of peritoneal dialysis, on the rate of residual renal function loss [70]. Davies et al. looked at the half-life of loss of residual renal function in 303 patients started on peritoneal dialysis between 1990 and 1997 [32]. Patients with interstitial nephritis, renovascular disease and hypertensive nephrosclerosis had slower decline of residual renal function. Comorbid conditions did not influence rate of loss of residual renal function. Moist et al. studied predictors of loss of residual renal function in new dialysis patients [40]. As partially mentioned before, increasing age, female gender, and nonwhite race predicted faster loss, whereas peritoneal dialysis and use of angiotensin converting enzyme inhibitors and calcium channel blockers was associated with slower loss of residual renal function. However, the primary outcome variable was urine volume, not residual glomerular filtration rate, in that study. Singal et al evaluated the risk factors assumed to be associated with residual glomerular filtration rate [75]. There was no effect of age, race, or primary renal disease on the rate of decline of residual renal function. Presence of diabetes as a cause of renal disease or as a comorbidity was significantly associated with the rate of decline. Presence of peripheral vascular disease and higher degrees of left ventricular dysfunction on echocardiography may have a significant effect in patients in upper and lower quartiles of slope of residual glomerular filtration rate. Considering the 105 patients with diabetes, 38% had peripheral vascular disease and left ventricular dysfunction of grades I to IV in 60%, 13%, 15%, and 12% of patients respectively; compared to 137 patients with no diabetes where 12% had peripheral vascular disease and left ventricular dysfunction of grades I to IV in 77%, 13%, 7%, and 3% respectively. Similarly, 24-hour urinary protein excretion may also be associated with diabetic nephropathy as a cause of end-stage renal disease.

Therefore, residual renal function may contribute significantly to total solute clearance and fluid balance in patients on continuous peritoneal dialysis. Changes in residual renal function with time are not uniform in all patients. Faster decline of residual renal function corresponds with male gender, large body mass index, presence of diabetes mellitus, higher grades of congestive heart failure and higher 24-hour proteinuria. Higher rates of peritonitis and use of antibiotics for the treatment of peritonitis are also associated independently with faster decline of residual renal function. Whether the type of peritoneal dialysis and use of

larger dialysate volume are associated with faster decline of residual renal function remains speculative [75]. In summary, loss of residual renal function and urinary output is an important risk factor of morbidity and mortality in dialysis patients. In predialysis patients, proteinuria is clearly associated with renal and cardiovascular disease progression. However, the link between proteinuria and residual renal function in dialysis is to be discussed next.

3. Proteinuria and chronic kidney disease

The incidence of end-stage renal disease is dramatically increasing worldwide [80]. Most patients with kidney problems visit their physicians in the late stages of the disease. Progression from mild to moderate kidney disease to end-stage renal disease may be halted or slowed when kidney damage is detected and appropriate treatment is started during the early stages. Kidney damage is frequently asymptomatic but can be suspected in the presence of proteinuria, hematuria, or a reduced glomerular filtration rate [81]. Due to increased awareness of people about chronic kidney disease and early detection and prevention programs implemented in developed countries, the incidence of end-stage renal disease has shown a small downward trend [82,83]. However the total number of individuals worldwide with chronic kidney disease is still high and estimated at 500,000,000 people [82-84].

Proteinuria is a major risk factor for renal disease progression [85-87]. Among the main causes that lead to dialysis, diabetes, hypertension and glomerular diseases account for more than 70% of the most frequent described etiologies in the adult population. All these entities display a marker of disease progression: Proteinuria. In this setting, proteinuria can be due to primary glomerulopathies, which is the third cause of end-stage renal disease in the adult population and an important cause of secondary hypertension, or could be the result of secondary glomerular damage due to primary hypertension, diabetes mellitus, hyperfiltration, metabolic syndrome, reduced renal mass, autoimmune or infectious diseases, vesicoureteral reflux, etc.

Proteinuria is another predictor of increased cardiovascular risk in the general population [88]. Numerous studies have shown that treating proteinuria in patients with diabetic or non-diabetic chronic kidney disease and proteinuria slows the progression of renal disease. It can also be stated that the greater the decrease in proteinuria, the greater the clinical benefit [89-91]. In addition to predicting kidney disease progression, proteinuria is a well-established risk marker for cardiovascular disease [86,92-94]. In chronic kidney disease individuals, reduction in proteinuria confers a significant decrease in cardiovascular events. For example, the RENAAL study showed that albuminuria is the most important factor in predicting the cardiovascular risk in patients with type 2 diabetic nephropathy, and at 6 months for every 50% reduction in albuminuria, a 18% reduction in cardiovascular risk and a 27% reduction in heart failure was reported[16]. It is evident that proteinuria presents an important predictive value in cardiac failure, both as a marker of future events and also as a therapeutic target. Patients with diabetic nephropathy and proteinuria greater than 3 g/g have a 2.7-fold higher risk for heart failure when compared with patients with low proteinu-

ria (<1.5 g/g) [95]. A coexistent diagnosis of hypertension and diabetes increases the risk of adverse cardiovascular and renal outcomes. This increased risk extends to a diastolic blood pressure of 83 mmHg and a systolic of 127 mmHg [96,97]. Reduction of proteinuria by >30% within the first 6 to 12 months of treatment in patients with chronic kidney disease has also been shown to predict long-term renal and cardiovascular outcomes [86,88,98]. Moreover, the management of albuminuria in normotensive or hypertensive patients with diabetes may slow progression of diabetic nephropathy [99], and microalbuminuria itself, an early marker of kidney vascular dysfunction, is a strong prognostic indicator of mortality and cardiovascular disease in hypertension and diabetes mellitus [100,101]. Therefore, one of the main goals to slow the progression of renal disease is an adequate and not unusually aggressive control of blood pressure and the reduction of proteinuria to its lowest possible level [102]. Moreover, proteinuria has been shown to be the strongest predictor of cardiovascular outcomes, including hospitalization for heart failure. Extinguishing proteinuria by decreasing blood pressure, hyperfiltration states, sodium intake, and tight glycemia control are generally accepted potential strategies to reduce cardiovascular risk events [89]. Although the nature of the links between proteinuria and vascular disease may partly be due to endothelial dysfunction, persistent low-grade inflammation also plays a role. Indeed, inflammation is associated with both endothelial dysfunction and albuminuria [11,102-104]

4. Residual renal function and proteinuria

The past 20 years of research in nephrology have yielded substantial information on the mechanisms by which persisting dysfunction of an individual component cell in the glomerulus is generated and signaled to other glomerular cells and to the tubule. Spreading of disease is central to processes by which nephropathies of different types progress to end stage renal disease. Independent of the underlying causes, chronic proteinuric glomerulopathies have in common a sustained or permanent loss of selectivity of the glomerular barrier to protein filtration. Glomerular sclerosis is the progressive lesion beginning at the glomerular capillary wall, the site of abnormal filtration of plasma proteins. Injury is transmitted to the interstitium favoring the self-destruction of nephrons and eventually of the kidney. The underlying mechanisms of tubulointerstitial injury that are activated by ultrafiltered protein load of tubular epithelial cells continue during the entire process of the disease, which is accompanied by several clinical markers, as fluid and toxins retention, edema, hypertension, proteinuria, creeping creatinine and a continuous decrease in urinary output. It needs to be emphasized that this field is relevant to interpret clinical findings and to improve treatment of patients with non-diabetic or diabetic nephropathies.

The opinion among nephrologists that proteinuria could be a marker only of injury largely has been challenged. The strong predictive value of proteinuria in chronic nephropathies now is firmly established. Baseline proteinuria was an independent predictor of renal outcome in patients with type 1 diabetes and nephropathy [105]. and in patients who did not have diabetes and entered the MDRD study [86]. In the Ramipril Efficacy In Nephropathy (REIN) trial [92], urinary protein excretion was the only baseline variable that correlated sig-

nificantly with glomerular filtration rate decline and progression of non-diabetic chronic proteinuric nephropathies to end-stage renal disease. Similar evidence was provided recently in patients with type 2 diabetes and overt nephropathy [87]. Other studies corroborated these data and extended the predictive value of proteinuria to risks for overall or cardiovascular mortality [106,107]. Clinical trials consistently showed renoprotective effects of proteinuria reduction and led to the recognition that the antiproteinuric treatment is instrumental to maximize renoprotection [86,92,94,108]. The MDRD study revealed tight association between reduction of proteinuria and decrease in rate of glomerular filtration rate decline [86]. Protection that was achieved by lowering blood pressure depended on the extent of initial proteinuria. The renoprotection that was conferred by angiotensin-converting enzyme inhibition in the REIN study was mediated by the drug's action of reducing urinary protein levels, to the extent that patients who were on ramipril had a better outcome paralleled by more reduction in proteinuria, whereas blood pressure was comparable to that of control subjects [92]. Angiotensin converting enzyme inhibitor–induced reduction in proteinuria was the strongest time-dependent covariate predicting slower progression to uremia. Finding that the rate of glomerular filtration rate decline correlated negatively with proteinuria reduction and positively with residual proteinuria provided further evidence for a pathogenetic role of proteinuria [109]. Likewise, trials in type 1 [94,110] and type 2 diabetes [111,112] documented that whenever proteinuria is decreased by treatments, progression to end-stage renal disease is reduced. As already mentioned, the Reduction of Endpoints in type 2 diabetes with the Angiotensin II Antagonist Losartan (RENAAL) study [111] in 1513 patients with type 2 diabetic nephropathy confirmed that more reduction in proteinuria by losartan invariably was associated with more renoprotection at comparable levels of blood pressure control. Beneficial cardiovascular effects of losartan also were driven by effects on urinary protein and largely depended on the amount of residual proteinuria. Similar results were found in the Irbesartan Diabetic Nephropathy Trial [112]. Finally, the Angiotensin-Converting-Enzyme Inhibition and Progression of Renal Disease study [113,114] confirmed that proteinuria is a strong risk factor for progression of chronic renal disease and that patients with more severe renal disease benefit most from angiotensin converting enzyme inhibitor therapy. Importantly, in no case from a was there a worsening in proteinuria that subsequently was associated with an improved outcome [115].

In progressive nephropathies, severe dysfunction of the glomerular capillary barrier to circulating proteins causes protein overload of tubular epithelial cells and intrarenal activation of complement that is responsible for spreading of injury to the tubulointerstitium. Drugs that block angiotensin II limit the abnormal passage of plasma proteins and are renoprotective. The podocyte is the primary site of antiproteinuric action through stabilization of podocyte–podocyte contacts and prevention of permselective dysfunction at the slit diaphragm. Although the abnormal passage of plasma proteins across the glomerular capillary wall is likely to be a factor that is responsible for further podocyte injury and progression to glomerulosclerosis [116], most of the available data highlight the mechanisms underlying proximal tubular cell activation and interstitial inflammation and fibrosis. The toxicity of albumin seems to be mediated by its initial endocytic uptake, although the importance of albumin itself *versus* protein-bound molecules in the induction of irreversible tubular dam-

age is not clear. Other molecules, including ultrafiltered transferrin and immunoglobulins, and the intrarenal complement and ammonium interactions could play relevant roles. Developments in these areas yield further support to design protocols in which drugs against secondary pathways of injury should be tested in association with drugs that limit the abnormal passage of proteins across the glomerular capillary barrier [117]. This statement must be borne in mind when considering treatment of proteinuria as the patient enters dialysis, as the already triggered pathologic pathways are perpetuated.

In this regard, the pathophysiological process that leads to end-stage renal disease where proteinuria is a hallmark is crucial to be followed and treated. As long as urinary output is present, all the severely damaged nephron structures may be still abnormally working, as hypertension and proteinuria are two clinical evident markers of renal disease virtually present in the vast majority of dialysis individuals.

5. Hemodialysis: Is there a role of proteinuria as a marker of disease?

Noteworthy, despite this active attempt to reduce proteinuria in pre-dialysis patients to delay disease progression, proteinuria appears to be forgotten or even ignored by nephrologists once a patient enters dialysis. However, its existence may certainly continue conferring the well-known inflammatory, catabolic, fibrinolytic and toxic effects on the endothelium that has been exerting in the pre-dialysis period [104,118,119]. Our group determined that the higher degrees of proteinuria in chronic hemodialysis patients are associated with inflammatory and cardiovascular markers of disease [120]. These results may also be related to the nutritional status and mortality rates.

In chronic kidney disease patients, proteinuria is a common event, irrespective of cause, and virtually all patients with chronic kidney disease present variable degrees of proteinuria [121]. However, in dialysis patients, the prevalence of proteinuria is unknown. In the present study, proteinuria was present in 87% of the hemodialyzed population. Noteworthy, despite significantly differences in proteinuria among the three groups, these changes were not accompanied by significant alterations in albuminemia or in cholesterolemia. This phenomenon could be attributed to the similar nutritional status the three groups displayed and to the use of statins in virtually all patients. In patients with proteinuria > 3/day, the two main causes of end-stage renal disease were diabetes nephropathy and primary glomerulonephritis, although no significant differences in the amount the proteinuria could be observed between both subpopulations. However, there was a significant increase in diabetic patients with heavy proteinuria in comparison to the other two groups, and a relative increase in the diabetic population was observed as proteinuria augmented. Proteinuric levels did not correlate with body mass index, the type of vascular acceses, and could not be attributed to hypertension or to hemodynamic fluctuations, as Pro-Brain natriuretic peptide (Pro-BNP) measurements were not different among the groups. There was a significant difference in the ultrafiltration rates, but we could not associate it to any of the variables under consideration, particularly with Pro-BNP or adiponectin, between which important

feedback regulations exist. Interestingly, as proteinuria worsened, a significant correlation developed between Troponin T, a cardiovascular biomarker, and C-Reactive Protein (CRP), an inflammatory marker. This interrelationship may suggest that proteinuria could interact as a covert and ignored culprit in the complex and chronic protein energy wasting syndrome dialysis patients live in, contributing to a higher risk of cardiovascular disease and inflammation as proteinuria rises.

In our own experience, in a one-year recruitment cross-sectional study where 265 chronic kidney disease patients were classified into the 5 stages according to K/DOQI guidelines, proteinuria was present in 204 subjects (76.98%) [122]. Interestingly, proteinuria significantly worsened as kidney function declined, and the highest rates of proteinuria were encountered in the most advanced stages of the cohort: Stage 3, 1.39+3.2 g/day (range: 0-21.6) in 80% of the 90 cases included vs stage 4, 1.87+0.99 g/day (range 0-5.1), which represented the 95% of the 37 individuals included in this group. In Stage 5D, proteinuria was present in 85% of the 60 patients included, and the mean level of proteinuria was 2.48+3.72 g/day (range 0-21.5). This level of proteinuria was significantly higher and different from stages 3 (p=0.001) and 4 (p=0.013). These findings underscore previous findings that demonstrated that proteinuria is associated with chronic kidney disease, that worsens renal function, and that it is highly prevalent in end-stage renal disease [89-91,121].

Cardiovascular disease in the main cause of death in the chronic population. However, cardiovascular disease can be the final pathophysiological pathway where many different entities may converge: Framingham factors, malnutrition, oxidative stress, calcium-phosphate metabolism, anemia, infections, inflammation. Although we have included many of the traditional Framingham risk factors in our study, only diabetes mellitus was significantly more frequent in patients with proteinuria > 3 g/day compared to the other groups. In chronic kidney disease, the main causes that lead to renal replacement therapies are diabetic nephropathy, hypertension and glomerulonephritis. In all these entities, cardiovascular disease is a major cause of morbidity and mortality, and proteinuria again plays a key role in these pathophysiological processes. In our study, higher degrees of proteinuria (> 3 g/day) significantly correlated with Troponin T and CRP, markers of cardiovascular stress and systemic inflammation. Which is the relationship among CRP, Troponin T and proteinuria in hemodialysis, if any?. Both CRP and Troponin T have been employed as markers of highly prevalent complications as inflammation and cardiovascular disease in dialysis subjects. CRP has been reported to be elevated in 30 to 60% of dialysis patients, and can be employed as a predictor of cardiovascular mortality in hemodialysis [123]. In addition, it has been established that troponin T levels are increased in subjects with renal failure, even in the absence of myocardial ischemia [124-125]. In fact, approximately 53% of patients with chronic kidney disease present with elevated troponin T without acute myocardial necrosis [126] As troponin T is normally cleared by the kidneys, it could be elevated in chronic kidney disease owing to delayed clearance [127]. However, other reasons could also explain the high troponin T levels, as left ventricular hypertrophy, congestive heart failure, and sepsis [125,126,128]. The combination of increased levels of CRP and troponin T levels are associated with an increased risk of death in chronic kidney disease [129]. Finally, Wong et al state that the posi-

tive correlation between Troponin T and CRP could be due to an inflammatory process that could induce a sub-clinical myocardial damage resulting from endothelial injury and atherosclerosis [130]. How does proteinuria fit into this process?: In dialysis, proteinuria could be an important cause of inflammation and of endothelial dysfunction and atherosclerosis and peripheral vascular disease as in previous stages of chronic kidney disease [91, 117, 131], triggering CRP and troponin T elevations. This situation could justify that as proteinuria worsens, the correlation we found between troponin T and CRP rises significantly. It has recently been published that in a murine model of spontaneous albuminuric chronic kidney disease, the systemic endothelial glycocalyx is altered in its glycosylated components due to proteinuria itself. Therefore, it becomes reasonable to speculate that as this meshwork of surface-bound and loosely adherent glycosaminoglycans and proteoglycans modulates vascular function, its loss could contribute to both renal and systemic vascular dysfunction in proteinuric chronic kidney disease, including dialysis patients [132].

Therefore, it ought to be reasonable to focus on proteinuria as a target to treat, as its decrease may portend a better care of residual kidney function and cardiovascular status in stage 5D subjects. However, once patients are started on dialysis, proteinuria generally appears to be ignored and forgotten as a potential factor of morbidity and mortality, as it occurs in predialysis subjects. Proteinuria may contribute to the burden of cardiovascular disease and should be a parameter to pay attention to in dialysis individuals. Finally, despite being on dialysis, proteinuria should be controlled as its persistence may hasten the loss of residual renal function, a relevant item to preserve at any price in this population.

Moreover, proteinuria is not only important as a marker of progression of renal disease, but it is also associated with catabolic processes, protein-energy wasting, hypoalbuminemia, and inflammation. All these processes are prevalent in the dialysis community [11,12,17]. However, the data relating proteinuria and hemodialysis is more than scant. In a work published by Goldwasser et al in 1999, in which they observed a rise in albumin and creatinine in those patients who entered dialysis after six months of treatment, they hypothesized that this phenomenon could be attributed, in part, to a better nutritional status, a gain in muscle mass, and to a decline in residual renal function [121]. This decrease in urinary output could consequently result in lower losses of protein in the urine. Finally, it is well known that as proteinuria progresses, and more importantly without any medical intervention focused specifically on it, parenchymal fibrosis ensues and residual renal function rapidly deteriorates.

One question that needs to be addressed for dialysis patients is the threshold above which proteinuria would be implicated in inflammatory processes and could have any implication or contribution in the development of cardiovascular disease. Should the levels of proteinuria be interpreted in the same way as in pre-dialysis subjects?. Our study suggests that as proteinuria increases, cardiovascular stress and inflammatory processes are more prone to be encountered. No data exists whether proteinuria should be treated in dialysis and, if that were the case, the level to pursue. Our data suggest that proteinuria should be treated, considering its association with inflammation and cardiovascular stress. Although, as mentioned above, angiotensin converting enzyme inhibitors or angiotensin II

receptor blockers could have modified the results, these drugs were employed homogeneously in the three groups.

Finally, we have observed (data not published) that at higher degrees of proteinuria, urinary output deteriorates faster. At similar initial urinary output rates, patients with proteinria > 3 g/day performed differently from those < 3 g/day: After three years of follow-up, patients with proteinuria > 3 g/day when entering hemodialysis were anuric and therefore had no residual renal function. Patients with proteinuria < 3 g/day still had residual renal function, and proteinuria did not worsen significantly during the time of follow-up. Whether this was be due to a higher proportion of diabetic patients, to higher degrees of proteinuria, or to other cofactors as previous administration of contrast agents or exposure to nephrotoxic drugs cannot be concluded from our data. Besides, in patients with heavy proteinuria a shorter time on hemodialysis trend was observed. Again, whether this phenomenon should be ascribed to diabetes mellitus itself, or to proteinuria could not be concluded. Interestingly, as mentioned before, in non-dialysis patients proteinuria in diabetics is associated with an increased risk of cardiovascular events and mortality [85-87,95-97]. However, we underscore the critical importance proteinuria may play on hemodialysis as a forgotten, overlooked marker of cardiovascular and inflammation.

Our experience, albeit limited, calls the attention of nephrologists to take proteinuria into account when a hemodialysis patient is assessed. Due to the small number of cases included in our recently published study, conclusions must be drawn cautiously. In this respect, the significant correlation found between CRP and Troponin T may be associated with heavy proteinuria, but other factors not assessed in this study may also be involved. We were unable to measure other inflammatory molecules as interleukin-6 and Tumor Necrosis Factor, or endothelial and procoagulant molecules as Plasminogen Activator Inhibitor-1, which are more sensitive than CRP and would have certainly added more information to the data presented in this study. Finally, no vascular arteriosclerotic parameters as pulse wave velocity were evaluated in our patients, which would have certainly enriched our primary findings. Moreover, as an observational study in a cross-sectional cohort, no follow-up with regard to patient prognosis, to the evolution of proteinuria and its correlation with other biomarkers, and to mortality rates could not be obtained. All these results require validation [120]. However, we believe this work is a call of attention to nephrologists regarding another important aspect of the characteristics of urinary output and residual renal function in dialysis patients.

6. Conclusions

Proteinuria is a strong predictor of chronic kidney disease progression. It is also an important marker of cardiovascular disease, both in patients with or without kidney disease. In hemodialysis individuals, urinary output is associated with morbidity and mortality. At higher levels of diuresis, there is a trend to lesser rates of hospitalization and a higher mortality. Most of renal functions are better preserved if associated with higher volumes of

urine. In this regard, proteinuria plays a critical role in renal fibrosis, stimulating sclerosis in the glomerular and in the interstitial compartments. This sclerosis causes in turn local ischaemia and further deterioration of kidney function, which can be clinically assessed with creeping of serum creatinine and a final decline in urinary output. This phenomenon is observed throughout the chronic kidney disease process, even at the dialysis setting. We have found that in chronic hemodialysis patients, at higher degrees of proteinuria, systemic markers of cardiovascular disease and inflammation are elevated. Albeit not proven yet, as proteinuria causes an eventual decline in renal function, and preservation of residual renal function is associated with higher survival rates in dialysis patients, proteinuria may be also associated with a decrease in urinary output and an increase in morbidity events and mortality in chronic hemodialysis.

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