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Original Research Article

Does Urinary Protein Excretion and Hypertension Significantly Correlate with Progression to End Stage Renal Failure?

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ABSTRACT

Aims: To identify the prognostic factors possibly related to end-stage renal failure development.

Materials & Methods: The prognostic factors affecting chronic renal failure progression were analysed in 456 patients aimed at verifying the role of protein restriction in slowing down or halting the progression of chronic renal failure. 311 patients completed the 24-month follow-up foreseen by the protocol and 69 reached an end-point. Using the Cox proportional hazard regression model, using a stepwise procedure in order to select only those factors, which are significantly associated with survival, made an inductive analysis on patient survival. For each individual risk factor, a univariate descriptive analysis of survival was performed using the Kaplan-Meier technique.

Results: Underlying nephropathy, baseline plasma creatinine, proteinuria, and plasma calcium were all shown to be related to end-stage renal failure onset. Hypertensive patients (mean blood pressure > 107 mmHg) had a worst cumulative renal survival but the degree of proteinuria was even more important as a prognostic factor of renal death than hypertension. The cumulative renal survival of patients whose proteinuria decreased during the trial follow-up was better than those of patients without changes. However, the interaction between baseline lying mean blood pressure and proteinuria was not significant.

Conclusions: Only primary renal disease and proteinuria were related to renal survival, being baseline plasma creatinine confounding factor. By blocking the possible causal role of proteinuria and hypertension, end-stage renal failure could be prevented in a significant percentage of patients.

Keywords: Blood Pressure; End-Stage Renal Failure; Proteinuria; Hypertension; Prognostic.

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INTRODUCTION

Identification of the cause of renal failure, as well as the secondary factors contributing to its progression, may help in preventing a deterioration in renal function. The mechanism involved in progression has been extensively investigated and it has been found that it involves a number of physiological and metabolic changes, which may contribute to glomerular destruction.[1] Moreover, it is still not clear whether the degree of renal impairment from the initial insult is more important than the underlying disease process and its persistent activity. Because progressive loss of renal function is often observed even when the underlying disease is no longer active, other factors may also contribute to renal disease progression and several intercurrent events may accelerate the rate of deterioration of renal function. The detection and correction of these events may slow the progression of chronic renal failure and delay the need for dialysis. Therapeutic interventions, such as protein and phosphate restriction, and the use of antihypertensive or other drugs, may play an important role. However, changes in the rate of progression may be unrelated to such interventions and a persistent slowing in the progression of renal function can also occur spontaneously.[2] This is of a paramount importance, because there could be a population of patients who do not require the prescription of careful protein restriction and/or drug administration in order to slow down or halt what is already a stable renal failure. Therefore it is important to identify the factors possibly related to end-stage renal failure development because

this could allow patients with progressive disease to be distinguished from those with non-progressive, or at least slow-progressive, disease. Non-progressive patients could be controlled simply by means of symptomatic and corrective treatment; therapeutic approaches (diet, drugs, etc.) designed to modify the course of the active disease could be limited to progressive patients. To try to clear this point, we have analysed data relating to 456 patients aimed at verifying the role of protein restriction in slowing down or halting the progression of chronic renal failure.[3] According to the protocol formal statistical analysis,[3] the actuarial renal survival rate was slightly higher (although of only a borderline significance) with the low-protein diet than with the controlled-protein diet for the whole trial population (27 versus 42 end-points respectively: P= 0.0596 Breslow, P= 0.0592 Mantel-Cox). As far as the fall in creatinine clearance and the rise in plasma creatinine are concerned, there were no differences between diets in their mean values in the total study population. Therefore, given the importance of other prognostic factors, which may be confounders, a multivariate analysis may clear the role of these risk factors of renal death.[3]

SUBJECTS AND METHODS

The inclusion criteria were cooperative out-patients (aged 18-65 years) with chronic renal failure, defined as plasma creatinine levels (PCr) ranging from 133 (119 in women) to 619 mmol/1 and a creatinine clearance (CCr) rate of < 60 ml/min (calculated according to Cockroft's formula).[4] The study population was stratified into three groups, according to the severity of renal function deterioration: group A (PCr l33-221 mmol/1), group B (PCr 222-442- mmol/1) and group C (PCr 443-619 mmol/1). The causes of chronic renal failure were glomerulonephritis in 132 patients (29%), nephroangiosclerosis in 72 patients (15.8%), interstitial nephropathies in 156 patients (34.2%), polycystic kidneys in 74 patients (16.2%), and other causes (Alport syndrome, malformations, etc.) in 22 patients (4.8%). The patients excluded were those with a variation in PCr of more than 100% during the 3-month preliminary observation period and patients with diabetes, nephrotic syndrome (defined as proteinuria > 3 g/24 h and serum albumin <2.5 g/dl), acute obstructions of the urinary tract, an ideal body weight <45 or >90 kg, acute infective diseases (including those of the urinary tract), systemic illnesses (such as autoimmune disorders and malignancies), any other condition requiring treatment with drugs theoretically affecting the progression of the underlying renal disease, and patients who had undergone previous surgery on the gastrointestinal tract.

Hypertensive patients (blood pressure > 150/90 mmHg) were treated with the following stepped care therapy:

(1) Beta blockers or, in case of contraindications, central antihypertensive agents;

(2) Calcium-channel blockers or other vasodilators;

(3) Frusemide.

The protocol recommended to avoid as much as possible ACE inhibitors and minoxidil because of their possible effect on renal function deterioration, and the use of vitamin D was not permitted. Calcium carbonate was recommended between meals in order to maintain total plasma calcium levels at between 2.25 and 2.75 mmo/1, and when necessary calcium carbonate or aluminium hydroxide during meals in order to maintain normal plasma phosphate levels. Severe hyperuricaemia was treated with allopurinol; uricosuric agents were not allowed. In the treatment of metabolic acidosis, calcium carbonate was supported by the administration of the lowest possible doses of sodium bicarbonate. The low-protein diet was designed to supply 0.6 g protein (0.5 animal) per kg ideal body wt/day, with an energy supply of 35-kcal/kg body wt/day; the controlled-protein diet supplied 1.0 g protein (0.6 animal) per kg ideal body wt/day, with an energy supplement of 30-kcal/kg body wt/day. Both dietary regimens were phosphate restricted, with a daily phosphate intake respectively of 8 and 12 mg/kg body wt/day. The low-protein diet included low-protein bread, pasta, and flour; the controlled-protein diet did not. In this study, the baseline value of plasma creatinine, phosphate, total calcium, total cholesterol and 24-h proteinuria were considered. After randomization a 2-year follow-up for each patient was planned.

Statistical Analysis

The need for dialysis or the doubling of baseline PCr considered as the trial end-points. Patient survival times were censored at the time of the end of the study follow-up, considering the doubling of plasma creatinine or the need for dialysis as the event. Sex, age (at protocol admission), underlying nephropathy, pretreatment risk factors (mean lying blood pressure, 24-h proteinuria, plasma levels of calcium, phosphate, and total cholesterol), as well as the prescribed diet (low-protein or controlled protein) were taken into account. Patient survival was evaluated using the Cox proportional hazard regression model,[5] using a stepwise procedure in order to select only those factors that were significantly associated with renal survival. The only formal tests of the whole statistical analysis are those performed on the parameters of the Cox model. The baseline plasma creatinine has been included into the Cox model in order to correct for its possible confounding effect. For each individual risk factor, a univariate descriptive analysis of survival was performed using the Kaplan-Meier technique. For this purpose the patients were stratified according to baseline proteinuria values into three strata, namely lower than 1 g/day, 1-3 g/day, higher than 3 g/day, and according to baseline mean blood pressure values into two strata, namely lower and equal or higher than 107 mmHg.

All the statistical analyses were made using SPSS (SPSS Inc.) and EGRET (Statistics and Epidemiology Research Corporation and Cytel Software Corporation) Statistical and Epidemiological Software packages.

RESULTS

Of the 456 patients who entered the trial (247 male and 209 female; mean age 48.5 years: range 18-65), 311 completed the period of observation foreseen by the protocol and 69 reached an end-point, 27 on the low-protein and 42 on the controlled-protein diet.[3] Of the 69 end-points, 47 reached the need for dialysis treatment. The actuarial renal survival rates (end-point: doubling of initial plasma creatinine or need for dialysis) in the patients stratified according to the underlying disease. Patients with polycystic kidney disease had the maximum probability of reaching an end-point. The actuarial renal survival rates according to the baseline 24-h proteinuria level: the probability of reaching an end-point became progressively higher going from the group with 24-h proteinuria lower than 1 g to that with 24-h proteinuria higher than 3 g. The cumulative survival curves according to the baseline lying mean blood pressure, lower or higher than 107

mmHg, show that patients with baseline lying blood pressure higher than 107 mmHg had a slightly lower survival rate than the others (i.e. 24-month cumulative survival 89 versus 80%).

According to the protocol Standard Operating Procedure, only 34 patients were treated with ACE inhibitors. Because of the low percentage of patients with baseline 24-h proteinuria higher than 3 g (9.3%), as a result of the protocol selection criteria, we did not descriptively analyse this patient group. The analysis of end-point renal survival curves according to the baseline 24-h proteinuria level (lower than 1 g and within the range of 1-3 g) and to the baseline lying mean blood pressure (lower or higher than 107 mmHg). Patients with the higher level of baseline lying mean blood pressure had a slightly worse renal survival in each 24-hour proteinuria strata.

Sex, age (at protocol admission), baseline creatinine, underlying nephropathy, pretreatment risk factors (mean lying blood pressure, 24-h proteinuria, plasma levels of calcium, phosphate and total cholesterol), as well as the prescribed diet (low-protein or controlled protein diet) were introduced by a stepwise procedure into a multivariate analysis. Baseline plasma creatinine, underlying nephropathy (nephroangiosclerosis and polycystic kidney disease had a relative risk of renal death respectively of 3.55 and 2.47 versus interstitial nephritis), 24-h proteinuria and plasma calcium were all significantly related to renal survival. **(Table 1)**

Table 1: Summary of risk factor analysis of renal survival

Parameters	Odd ratio	95% confidence interval		P value
		Lower	Upper	
Plasma creatinine	2.178	1.831	2.593	0.001
24-h proteinuria	1.500	1.261	1.785	< 0.001
Plasma calcium	0.780	0.655	0.929	0.005
CGN/IN	1.132	0.560	2.287	NS
NAS/IN	3.554	1.524	8.287	0.003
PCK/IN	2.466	1.100	5.532	0.028

Sex, age, mean lying blood pressure, plasma phosphate and total cholesterol were not significantly related to renal survival, and therefore are not included into the reported model. In order to try to clarify the importance of the behaviour of proteinuria and hypertension and their relationship as factors of chronic renal failure progression, the patients with baseline 24-h proteinuria higher than 1 g and mean blood pressure higher than 107 mmHg were stratified into four subgroups according to the behaviour of 24-h proteinuria and mean blood pressure values during study follow-up. The first group with no changes in 24-h proteinuria and mean lying blood pressure from baseline during the follow up, the second group with a clinically significant (>5mmHg) mean blood pressure decrease, the third group with a clinically significant 24-h proteinuria decrease (>30%), the fourth group with a mean blood pressure and a 24-h proteinuria decrease. Only in 13% of these patients (subgroup 1) did the mean blood pressure or/and proteinuria levels during the follow up not decrease. Therefore the size of this subgroup is too small («= 10) to allow an analysis. The descriptive analysis of renal survival according to the original endpoints shows that only the decrease of proteinuria affects renal survival, whereas the simultaneous decrease of proteinuria and mean blood pressure did not seem to give a further benefit.

DISCUSSION

The clinical trials aimed at assessing the effect of a therapeutic regimen in halting or slowing down the progression of chronic renal failure is surely complex and costly. Therefore it is of paramount importance to identify the baseline prognostic factors related to renal survival and the factors whose modification during the trial follow-up could affect chronic renal failure progression. Moreover, it is important to check the degree of modification of these clinical and biochemical parameters necessary to reach the best results and especially the mechanism of the relationship among these factors of progression and their behaviour. All the tested variables may act as confounders of one another; therefore an analysis of the effect of all the possible prognostic factors should keep all of them simultaneously into account. This is why we chose the Cox proportional hazard model to measure the relevance of each single prognostic factor in a situation where all the others are kept constant. The statistical analysis of the parameters of Cox model tests the hypothesis that the hazard ratio is different from 1, namely that the effect is present. Moreover, in our study the univariate descriptive analysis of survival was performed just to give a visual feeling of the size of the phenomena analysed; however, their exact magnitude should be drawn from the estimated hazard ratios of the Cox model.

The results of this trial clearly suggest that the primary renal disease is a very important factor of progression, showing polycystic kidney disease and glomerulonephritis more progressive than nephroangiosclerosis and interstitial nephritis. The results also confirmed the importance of baseline level of renal function as related to the reach of an endpoint. This is an expected result, as the protocol formerly established three plasma creatinine level strata. However, it is important to stress that the baseline plasma creatinine has been included into the Cox model not because of its interest as prognostic factor, but to eliminate its possible confounding effect. Proteinuria was highly significantly related to renal survival,: the cumulative renal survival is getting worse and worse going from proteinuria levels of less than 1 g/24 h to more than 3 g/24 h. This is a very important finding because the limit of 24-h proteinuria established by the inclusion criteria of the trial (lower than 3 g/24 h) possibly blunted the effect. These results are in agreement with the findings of Williams et al.[6] and Hunt et al.[7] who showed that the higher the level of urinary protein excretion, the steeper the slope of renal function decline. However, it is unclear whether proteinuria is only a marker of a more active underlying disease or a direct cause of functional deterioration.[6-10]

It is important to stress that the cumulative renal survival of patients whose proteinuria decreased (either spontaneously or because of antihypertensive therapy) during the trial follow-up was better than those of patients without changes, whereas the patients with a simultaneous decrease of proteinuria and blood pressure did not show any further benefit. This descriptive observation is in agreement with the results of Apperlo et al.[8] who reported that the treatment induced fall in urinary protein excretion is associated with a better renal functional outcome. Thus the lowering of proteinuria may possibly help to prevent a progressive renal function decline. The results of multivariate analysis (Table 1), after having taken into account the underlying renal disease, baseline renal function (plasma creatinine), baseline 24-h proteinuria, and plasma total calcium, show that nephroangiosclerosis is as progressive as polycystic kidney disease (95% confidence intervals of renal death relative risk are respectively 1.52-8.29 and 1.10-5.53 versus interstitial nephritis).

The glomerulonephritis shows a statistically non-significant higher relative risk than interstitial nephritis. We have to stress the usual reservation due to the reliability of the underlying disease diagnosis. Otherwise, it is clear that the distribution according to the baseline 24-h proteinuria level was not homogeneous; in fact patients with baseline proteinuria of more than 1 g/day were 38% of the total study population, but 60% of patients with glomerulonephritis. This hazard ratio of the patients with glomerulonephritis as against those with interstitial nephritis results from the correction of the unbalanced distribution in terms of 24-h proteinuria. Moreover, patients with polycystic kidney disease (accounting for 16.2% of the total study population) had a high risk of renal death in an univariate way. The fact that the distribution according to the baseline renal function level was not homogeneous (patients with polycystic kidney account for 34% of those of group C, with baseline PCr 443-619 mmol/1) could be a very important confounder. In fact after having taken into account the different baseline levels of renal function in the multivariate analysis, it is not surprising that the patients with polycystic kidney disease had a relatively lower risk of renal death. Blood pressure is generally believed to be related to renal survival. Many patients with progressive chronic renal disease suffer from hypertension and proteinuria. In our trial the descriptive analysis seems to stress the relationship between blood pressure and renal survival.

However, the baseline lying mean blood pressure was not significantly related to renal survival using the multivariate analysis. To evaluate the possible relationship between proteinuria and hypertension in chronic renal failure progression, the cumulative renal survival after having divided the patient into hypertensives (mean blood pressure > 107 mmHg) and normotensives (mean blood pressure < 107 mmHg) and according to different levels of proteinuria (< 1 g/24 h and in range 1-3 g/24h), was analysed. The interaction between baseline lying mean blood pressure and a 24-h proteinuria, that is the change in the relative blood pressure renal death risk when there is a difference in proteinuria, was not significant. This result could be due to the narrow range of 24-h proteinuria established by the trial. In fact if the effect of blood pressure is related to proteinuria, a direct relationship between blood pressure and progression of chronic renal failure would be possibly detectable only in heavy proteinuric strata. It has been reported that the lowering of blood pressure per se, not only in diabetic,[11] but also in non-diabetic renal disease,[12] reduces the decline in renal function. Recently Klahr et al.[13] showed that patients with a higher degree of proteinuria had a faster decline in the glomerular filtration rate and a better benefit of the lowering of blood pressure was apparent at 3 years, even lowering blood pressure below the usually defined upper limit of normal range.

The initial total plasma calcium level, but not plasma phosphate, was significantly inversely related to renal survival. Williams et al.[6] found only a weak correlation between calcium-phosphorus product and rate of renal function, while Gretz et al.[14] showed no relationship between serum phosphate and progression of renal failure, although over a much wider range of renal function. In animal models renal failure may progress also through interstitial deposition of calcium phosphate salts,[15] thus justifying the prescription of a low-phosphorus diet. Therefore the inverse relationship between total calcium level and renal survival is conflicting. Once again, proteinuria could play a key role because of the relationship between marked proteinuria, decreased plasma albumin level, and low total plasma calcium. On the other hand, although the relationship between proteinuria and high plasma cholesterol level is well known,[16] cholesterol was not significantly related to renal survival. As far as the effect of the prescription of a low-protein diet is concerned, multivariate analysis, after taking into account the reported prognostic factors, confirmed that the results of our trial offers little, if any, support to the view that low-protein diet prescription helps to delay chronic renal failure progression as against a controlled-protein diet prescription.

CONCLUSION

Primary renal disease and proteinuria were related to renal survival, being baseline renal function more confounding than prognostic factor. The lowering of proteinuria may possibly help to prevent the end-stage renal failure development, but the open question is the causal nature of this relationship.[17]

The descriptive analysis seems to support the relationship between blood pressure and renal survival while the multivariate analysis did not. The interaction between baseline mean blood pressure and 24-h proteinuria was not significant. The effects of any medical intervention (diet or drug) in slowing down the progression of chronic renal failure is more evident in terms of years of delay of end-stage renal failure needing a replacement treatment in the early phases, though the benefit in percentage is the same.

By blocking the possible causal role of proteinuria and hypertension, the end-stage renal failure could be prevented in a significant percentage of patients. Once the efficacy of such therapy is clearly stated, this procedure should be started in the early stages of chronic renal failure.

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