

Proteinuria

A pathogenetic role for proteinuria in progressive loss of renal function is suggested by many experimental studies involving renal damage of diverse origin. In ablation models, proteinuria is closely associated with glomerular hypertension, presumably reflecting the severity of hypertension-induced renal damage. Studies in experimental nephrotic syndrome caused by puromycin nucleoside or doxorubicin (Adriamycin) have demonstrated that in these models, proteinuria precedes progressive glomerulosclerosis in the absence of glomerular hypertension.^[103] Taken together with studies on the tubulotoxicity of the components of proteinuric urine, these studies provide evidence that proteinuria as such can be an independent pathogenetic factor in progressive renal structural damage.

In humans, the severity of proteinuria appears to correlate well with the severity of glomerular sclerotic lesions in such diverse renal conditions^[104] as IgA nephropathy,^[105] preeclampsia,^[106] diabetic nephropathy,^[85] human immunodeficiency virus-induced nephropathy,^[107] crescentic glomerulonephritis,^[108] unilateral agenesis or surgical removal of renal tissue,^[109] ^[110] reflux nephropathy,^[111] and hypertensive nephropathy,^[112] as reviewed elsewhere.^[113] Moreover, proteinuria consistently predicts the subsequent rate of loss of

Figure 56-7 Time course of glomerular filtration rate (GFR) before, during, and after withdrawal of antihypertensive therapy in renal patients. *Closed circles and continuous lines* are patients who initially showed a distinct fall in GFR ($n = 20$). *Open circles and broken lines* are patients in whom the GFR did not fall at the start of therapy ($n = 20$). After withdrawal of therapy, a rise in GFR occurs in patients with an initial drop only, thus demonstrating the functional nature of the initial drop in GFR. Interestingly, withdrawal of treatment reveals that the GFR is better preserved in patients with an initial drop. (Used with permission from Apperloo AJ, de Zeeuw D, de Jong PE: A short-term antihypertensive treatment induced fall in glomerular filtration rate predicts long term stability of renal function. *Kidney Int* 51:793–797, 1997.).

renal function in many renal conditions^[6] ^[42] ^[114] ^[115] and is the best predictor of end-stage renal failure.^[116] This relationship has been found not only in populations with renal conditions of diverse origin—where it might reflect differences in prognosis between different disorders—but also in homogeneous populations such as those with IgA nephropathy,^[117] diabetic nephropathy,^[74] ^[118] membranous glomerulopathy,^[119] ^[120] atherosclerotic renal disease,^[121] and immune-mediated renal disease such as Wegener granulomatosis.^[122] Remarkably, the association between proteinuria and the rate of progression is present not only in conditions in which proteinuria might reflect the severity or activity of a primary glomerular disorder but also in chronic pyelonephritis^[6] and vesicoureteral reflux.^[123] ^[124] Thus, proteinuria, once present, is a major risk factor for progressive loss of renal function across a spectrum of renal disorders. This consistent

relationship fueled the hypothesis that proteinuria is a key factor in a vicious circle of non-disease-specific factors that account for progressive renal function loss.^[4] Because many patients progress toward end-stage renal failure without significant proteinuria, however, its impact relative to disease-specific factors may vary between different populations. Jungers and colleagues^[125] as well as Williams and associates^[6] reported that both proteinuria and the underlying disorder were independent determinants of the rate of progression, whereas Wight and co-authors reported that differences in the progression rate between different renal disorders—except for polycystic kidney disease—were no longer apparent after correction for proteinuria.^[44]

Reduction of Proteinuria

Intervention studies support a pathogenetic role of proteinuria in progressive loss of renal function in experimental as well as human renal disease. In comparative studies, antihypertensive regimens associated with a better reduction in proteinuria provided better renoprotection in both diabetic^[67] ^[126] and nondiabetic nephropathy.^[65] ^[127] ^[128] ^[129] ^[130] This finding may not be limited to over proteinuria or hypertension because studies of patients with NIDDM have revealed that the association between the reduction in albuminuria and the long-term course of renal function was also present in normotensive, normoalbuminuric patients.^[68] The association between a reduction in proteinuria and renal prognosis applies not only to antihypertensive treatment but also to remission of proteinuria attained spontaneously,^[106] ^[107] by immunosuppressive treatment,^[131] or by the nonsteroidal anti-inflammatory drug (NSAID) indomethacin.^[132]

Interestingly, in individual patients, the course of long-term renal function correlates with the antiproteinuric response to therapy.^[133] In patients with an effective antiproteinuric response that results in lower residual proteinuria during treatment, the long-term course of renal function is more favorable than in patients with a less pronounced antiproteinuric response, as shown in many studies.^[42] ^[68] ^[134] ^[135] ^[136] ^[137] ^[138] ^[139] ^[140] ^[141] ^[142] For clinical purposes, it is important that this correlation already be apparent early after the start of therapy to allow early distinction between patients who will benefit from the intervention and those in whom the intervention will not be effective for long-term renoprotection—specifically, patients who need additional therapy. Of note, with the exception of the MDRD study, such a predictive value was not present for the blood

pressure response, thus supporting an independent role of proteinuria. The predictive value is present in both diabetic and nondiabetic patients and appears to be independent of the severity of baseline proteinuria or albuminuria ([Fig. 56-8](#)). It also appears to be independent of the mode of therapy because it was found in studies with different antihypertensive regimens, as well as in populations treated with a single regimen. Moreover, the predictive value was also present with nonpharmacologic reduction of proteinuria by a low-protein diet.^[100] Animal experiments have shown that the efficacy of the initial reduction in proteinuria also predicts protection against the development of

structural renal damage (i.e., focal glomerulosclerosis).^[143] In humans, however, similar data on protection against renal structural damage are not available.

The consistent relationship between residual proteinuria and long-term renal prognosis demonstrates first and foremost that a reduction in proteinuria is a prerequisite for renoprotection; moreover, this relationship supports the hypothesis that proteinuria plays a causal role in progressive loss of renal function. Additional support is provided by the correlation between residual proteinuria during treatment and the rate of progression.^[137] However, the evidence is not conclusive. A valid assessment of the severity of renal damage before

Figure 56-8 A, Correlation between residual proteinuria after stabilization of the antiproteinuric response (x axis) and rate of subsequent renal function loss (glomerular filtration rate [GFR] slope, y axis): $r = 0.62$, $P < .0004$; $r = 0.43$, $P < .025$ if the right-side outlier is omitted. **B**, The correlation between the reduction in proteinuria from pretreatment values (percent change in proteinuria; x axis) and rate of subsequent renal function loss (GFR slope, y axis) in the same patients; $r = 0.47$, $P < .011$. (Adapted with permission from Apperloo AJ, de Zeeuw D, de Jong PE: Short-term antiproteinuric response to antihypertensive therapy predicts long-term GFR decline in patients with non-diabetic renal disease. *Kidney Int Suppl* 45:174–178, 1994.)

intervention—which might determine both the antiproteinuric response and the subsequent rate of renal function loss—is difficult to obtain in humans. Uncontrolled, retrospective data in human transplant recipients suggest that pretreatment renal interstitial damage is a determinant of the antiproteinuric efficacy of ACE inhibition,^[144] a finding supported by prospective animal data.^[145] Moreover, it is hard to envisage how a reduction in normoalbuminuria to even lower levels, as reported by Ravid and colleagues,^[68] in itself would exert a renoprotective effect. Finally, perhaps the most important piece of evidence that is lacking are studies deliberately attempting to improve antiproteinuric efficacy to assess whether it would afford additional renoprotection. In studies evaluating the renoprotective potential of antihypertensive agents, either a fixed dose was used or treatment was titrated to obtain a target blood pressure level. In the study of El Nahas and associates on the renoprotective potential of protein restriction, standardized regimens were also used rather than titrating for given target criteria.^[100] In view of the consistent relationship between a reduction in proteinuria and renoprotection, as well as the absence of a J-shaped curve for proteinuria, exploration of the renoprotective potential of a treatment regimen titrated to obtain a maximally effective

reduction in proteinuria might be a fruitful approach to improve renoprotection.