NEFROLOGIA. Vol. XII. Supl. 5. 1992

EDITORIAL

The Progression of Chronic Renal Disease

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In most forms of chronic renal disease glomerular filtration rate (GFR) tends to decrease inexorably once a certain threshold of nephron destruction has occurred. The progressive decrease in GFR is accompanied histologically by increasing glomerulosclerosis and interstitial fibrosis, in which specialized segments of the nephron are progressively replaced by extracellular matrix[1]. Renal diseases of diverse etiology culminate in nephrosclerosis, the hallmark of the end-stage diseased kidney. This suggests that a heterogenous array of initiating insults can induce pathologic responses that converge upon a common avenue in which normal renal tissue is replaced by nonfunctional elements.

The mechanisms underlying the progression of renal are complex and very likely multifactorial[2]. Histologic similarities between glomerulosclerosis and atherosclerosis are striking and have led to the suggestion that both lesions share a common pathogenesis[3,4]. Factors that may participate in the development of atherogenesis include endothelial cell injury, lipid deposition, macrophage infiltration, cellular proliferation, and connective tissue deposition[5,6]. Similar factors may be responsible for the development of glomerulosclerosis. In addition, it should be remembered that mesangial cells closely resemble vascular smooth muscle cells[7].

The progression of chronic renal disease is mostly likely mediated by several risk factors acting alone or in combination. Potential risk factors that may contribute to the progression of chronic renal failure include systemic hypertension, proteinuria, hyperlipidemia, high protein or phosphorus intake and probably conditions that promote glomerular hypertrophy. Therapeutic maneuvers designed to minimize the potential contributions of one or more of these risk factors may halt or decrease the loss of renal function.

Assessing the Progression of Renal Disease

The progression of chronic renal failure is best assessed by sequential measurements of glomerular filtration rate (GFR) using exogenous markers such as inulin, ^{125}I-iothalamate, ^{99}Tc-DTPA, or ^{51}Cr-EDTA[8]. However, clinically the use of exogenous markers is not practical. Instead, the clearance of endogenous creatinine has been used to assess GFR[9]. Creatinine is not an ideal filtration marker in humans[10]. It is excreted both by glomerular filtration and by tubular secretion. Creatinine clearance overestimates GFR in normal individuals and this difference increases as chronic renal failure progresses. This is due to greater tubular secretion of creatinine as renal function decreases. Hence, the relationship between creatinine clearance and serum creatinine levels varies; as a consequence, the relationship between GFR and serum creatinine level varies. Nonetheless, the serum creatinine concentration remains the most widely used measure of progression of renal disease in clinical practice and in clinical trials. It should be remembered that the levels of serum creatinine are influenced not only by the level of GFR but also by muscle mass and dietary intake of meat[10].

Systemic hypertension

Systemic hypertension, whether primary or secondary, may cause renal disease or may accelerate the loss of function in kidneys with established parenchymal disease[11].

Hypertension may damage the kidney by increasing arteriolar wall thickness leading to ischemia and subsequent glomerulosclerosis, or it may damage the glomeruli directly through increased intraglomerular pressure[11]. Although careful documentation of the effects of control of blood pressure on the progression of renal disease in humans is limited, most of the evidence suggests an important role of hypertension in the progression of chronic renal failure.

Hypertension in patients with chronic renal disease is correlated with the decrease in renal function[12]. Although several of antihypertensive agents may slow the progression of renal disease, inhibitors of the angiotensin converting enzyme (ACE) have a more specific benefit in reducing renal injury, but definitive clinical evidence supporting a differential effect is lacking. ACE inhibitors have been reported to influence favorably the course of a variety of renal diseases in man including primary glomerulopathies, diabetes mellitus, systemic lupus erythematosus, hypertensive renal disease, polycystic kidney disease and chronic pyelonephritis[13-16]. In most cases, converting enzyme inhibition was associated with a reduction in pro-

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teinuria[17, 18], and in some cases with a slowing in the rate of progression of renal disease. However, most studies have not examined an optimal control population to differentiate between the effects of blood pressure reduction and a more specific effect of ACE inhibitors on renal function.

Several studies have compared the effect of ACE inhibitors and other agents on the progression of renal disease. Ruilope et al.[19] examined the rate of progression of renal disease in 10 patients treated for 12 months with captopril, and compared it to their previous rate of progression while they were receiving an antihypertensive regimen consisting of propranolol, hydralazine, and furosemide. These investigators found a decrease in the rate of progression of the renal disease with converting enzyme inhibition. The use of the patients' previous rate of progression complicates the interpretation of the result of this study as unidentified «time» effects may be associated with slowing of progression[20]. Heeg et al.[21, 22] also compared the antiproteinuric effects of the converting enzyme inhibitor lisinopril with prior therapy with methyldopa and other conventional agents and demonstrated a more consistent reduction in proteinuria after ACE inhibition.

In patients with essential hypertension, treatment with an ACE inhibitor (captopril) reduced microalbuminuria whereas no change in albumin excretion occurred in a separate group of patients treated with β-blockers and diuretics[23]. Comparison of different agents in normotensive diabetic patients with microalbuminuria have yielded somewhat conflicting results: some studies demonstrate a beneficial effect of ACE inhibitors while other studies have not demonstrated a differential effect[24, 25]. The issue is further clouded by the demonstration of a significant slowing of the progression of diabetic kidney disease by regimens without converting enzyme inhibitors and by the ability of these regimens to reduce proteinuria[20, 26, 27]. Therefore, the question of whether there are differential effects of antihypertensives on renal injury has not been answered in a definitive way.

A significant correlation was found between the degree of reduction in mean arterial blood pressure and the decrement in the rate of loss of renal function[20]. Successful treatment of hypertension with propranolol slowed the rate of progression in patients with glomerulonephritis[28] and Brazy et al.[29] similarly found that patients successfully treated for hypertension had a slower rate of progression. Thus, a reduction in blood pressure is accompanied by a decrease in the rate of progression of renal disease. Yet, none of these observations fully resolve what is the association between hypertension and rapid progression; that is, the blood pressure improvement might be the consequence of and not the cause of a slower course in the progression of the underlying renal disease. It appears, therefore, that in diabetic and non-diabetic nephropathies treatment with ACE inhibitors controls systemic hypertension, reduced proteinuria, and slows the progression of the underlying renal failure[13-17]. It has been suggested that the effect of ACE inhibitors on the progression of diabetic nephropathy is unrelated to its hypotensive effect. This is difficult to ascertain without prospective randomized studies comparing ACE inhibitors to other antihypertensive agents. Animal studies have suggested that reduction of glomerular capillary pressures may protect residual renal function and that ACE inhibitors and calcium channel blockers may be particularly effective in reducing the progression of kidney disease through such a mechanism[2].

Several studies suggest that reduction of diastolic blood pressure to levels less than 90 mmHg should be the goal of antihypertensive therapy in patients with established hypertension. All these trials were conducted in patients with essential hypertension. In a recent study[30] renal disease progressed even with «good control» of blood pressure. At least two explanations may account for this observation: 1) other factors besides elevated blood pressure had a role in the progression of renal disease in these patients; 2) lowering blood pressure to levels ≤140/90 mmHg may not prevent the untoward effect of hypertension on the kidney. In the pilot phase of the Modification of Diet in Renal Disease Study[31] there was a significant correlation between blood pressure levels and the decrease in GFR. The decrease was greater in patients with higher blood pressure. This correlation persisted even in patients whose blood pressure was below 140/90 mmHg. This observation suggests that it may be necessary to reduce blood pressure below this widely accepted target level to preserve renal function in patients with chronic renal disease. In patients with renal disease the capacity of the afferent arteriole to vasoconstrict in response to elevations in blood pressure may be abnormal and transmission of pressure to glomerular capillaries may cause «damage» even at levels of blood pressure considered adequate. Therefore, the «target» level for adequate control of blood pressure in patients with chronic renal failure needs to be defined.

Angiotensin II has other effects that may affect the course of chronic renal disease. Renal growth, particularly of the glomerulus, glomerular enlargement may predispose to injury[32]. Angiotensin II promotes growth of a number of cells and tissues including vascular smooth muscle, adrenal cortex, heart, and kidney[33-36]. In the kidney angiotensin II induces hypertrophy of proximal tubular cells and potentiates the mitogenic response of these cells to epidermal growth factor[36, 37]. In mesangial cells, angiotensin II increases ^{3}H-thymidine incorporation, induces hypertrophy, and stimulates collagen and actin synthesis[38-40]. In vivo, intrarenal infusion of angiotensin II increases the expression of several early growth response genes, an effect associated with cellular growth in other tissues[41]. Besides its direct effects angiotensin II promotes renal growth through its ability to stimulate ammoniagenesis in renal tubular cells[42]. Ammonia stimulates renal tubular hypertrophy[43]. Also, increased concentrations of ammonia in the renal cortex can induce tubulointerstitial disease by interacting with the C3 component of comple-

ment, resulting in activation of the complement cascade[44]. Angiotensin II also affects mesangial trafficking leading to increased uptake of macromolecules in the mesangium, which may predispose to eventual glomerular sclerosis[45]. Thus, angiotensin II could contributed to the progression of renal disease through both its hemodynamic and non-hemodynamic actions.

Proteinuria

The concept that proteinuria may be injurious to the glomerulus derives from the finding that the infusion of large amounts of heterologous albumin into normal animals produces an «overflow» proteinuria that persists after the foreign protein has been excreted. There is vacuolization of glomerular epithelial cells, fusion of foot processes and focal sclerosis the severity of which depends on the degree and chronicity of proteinuria[46]. Progression to renal failure in the absence of proteinuria is extremely rare in glomerular disease. This may indicate that marked proteinuria is a sign of more severe and eventually progressive disease, or that profuse proteinuria is of itself injurious and has a role in accelerating the original disease process or the development of glomerulosclerosis. Several retrospective studies indicate a worse prognosis for the development of end-stage renal failure in patients with severe glomerular disease and profuse continuing proteinuria[47]. Thus, maneuvers designed to diminish or abolish proteinuria may have a beneficial effect on the progression of chronic renal disease. Prospective clinical studies examining this issue have not been conduced.

It would seem appropriate, however, to decrease the degree of proteinuria since many of the manifestations of the nephrotic syndrome (hypoalbuminemia, edema, hyperlipidemia) are related to protein losses in the urine. Depending on the etiology of the renal disease, proteinuria may be responsive to the administration of corticosteroids, immunosuppressive agents (cyclophosphamide, immuran, cyclosporine) or the use of other drugs such as non-steroid anti-inflammatory agents (indomethacin). ACE inhibitors appear to be more effective than other antihypertensive agents in reducing proteinuria[18]. Low-dose captopril reduced proteinuria in diabetics[48] and non-diabetic patients with nephropathy without affecting blood pressure. Thus, some of the effects of ACE inhibitors in the progression of renal failure may relate not only to control of blood pressure but also to diminished proteinuria.

It has been postulated that proteinuria results in the liberation of fatty acids during the reabsorption and catabolism of protein, particularly albumin by proximal tubular cells. One or several of these fatty acids may act as chemoatractants for macrophages and bad to infiltration of the renal parenchyma by mononuclear cells. Macrophages, when activated, release a number of cytokines and growth factors that may influence and deposition of extracellular matrix and hence affect the progression of renal disease.

Hyperlipidemia

Numerous animal studies now exist to support a role of dietary induced hypercholesterolemia in the pathogenesis of progressive glomerular injury leading to focal glomerulosclerosis (FGS)[49-54]. Hypercholesterolemia as a secondary consequence of glomerular proteinuria also appears to participate in progressive glomerular damage[55-57]. Thus, experimental data would seem to indicate that primary, as well as secondary hyperlipidemia, contribute to the pathogenesis of glomerular injury.

Various animals models of endogenous hyperlipidemia are known to develop progressive glomerular injury[55-57]. Imai et al. described a strain of Sprague-Daily rats with spontaneous hypercholesterolemia which developed moderate proteinuria and FGS by 9 months of age[55]. Rats with the highest plasma cholesterol had the most significant reduction in renal function and the greatest degree of glomerular injury. Male rats had a significantly greater incidence of FGS than female rats. Not surprisingly, male rats had the highest serum cholesterol.

A number of studies have demonstrated that models of obesity and hyperlipidemia are associated with progressive glomerular injury[57-60]. Zucker fatty rats have features of noninsulin-dependent diabetes mellitus[61], such as insulin resistance in muscle and adipose tissue, mild glucose intolerance, pancreatic beta-cell hypertrophy, obesity, and hyperlipidemia[62, 63]. Both proteinuria and progressive glomerular injury were noted to develop after hyperlipidemia occurred. There were no changes in single nephron GFR or, intraglomerular pressure prior to the development of injury[58]. Thus, in this model, hemodynamic factors did not appear necessary for the development of glomerular injury. Importantly, two structurally unrelated lipid-lowering drugs (lovastatin and clofibrate) significantly reduced proteinuria and glomerular injury without altering glomerular hemodynamics[64]. These data suggested a pivotal role for lipid abnormalities in the pathogenesis of glomerular injury in the obese Zucker rat.

In studies of the nephrotic syndrome induced by PAN, reduction of circulating lipids by cholestyramine[65] or lovastatin[66] have been shown to reduce glomerular injury and preserve renal function. Thus, in models with hypercholesterolemia as a primary abnormality or in models with abnormalities of lipids ocurring as a consequence of renal disease, pharmacologic modification of plasma lipids resulted in amelioration of glomerular injury. No comparable data on the role of hyperlipidemia on the progression of renal disease in humans are available.

Effects of protein and phosphorus intake

Studies in animals[2] and clinical trials in humans[67-70] with chronic renal disease suggest that the dietary restriction of protein and phosphorus may slow the rate of progression. However, the trials of low-protein, low-phosphorus diets

in humans have generally been deficient with respect to experimental design. The deficiencies include the lack of proper randomization procedures, absence or inappropriateness of control population, use of retrospective data, inadequacy of methods of assessing renal function, and incompleteness of information about patients' adherence to the prescribed diet. Previous clinical trials[67] have also failed to document clearly whether such restricted diets maintain adequate nutrition and well-being in patients with chronic renal disease. A current clinical trial in the United Stated, the Modification of Diet in Renal Disease Study (MDRD) is examining in a cohort of 840 patients with chronic renal disease for effects of dietary protein and phosphorus restrictions on the progression of renal disease.

The full-scale trial will test primary hypotheses related to diet: first, that a diet low in protein and phosphorus will retard the rate of progression of renal failure in patients with chronic renal disease; second, that such a diet will not cause malnutrition; and third, that such a diet will be acceptable to patients over the long term. In addition, the full-scale trial will test two primary hypotheses regarding lowering blood pressure: that lowering the mean arterial pressure to 92 mmHg or below will reduce the rate of progression of chronic renal disease, and that such rigid blood pressure control will not be associated with an unacceptable increase in medication, hypotensive side effects, or both. Finally, the cost effectiveness of nutrition therapy in chronic renal disease will be studied to determine whether such therapy, if successful, should be made generally available under the Social Security Act. The study design in Phase III includes two groups based on the level of the glomerular filtration rate. In Study A, a diet with a moderate amount of protein and phosphorus will be compared with a diet low in protein and phosphorus in patients 18 to 70 years of age with glomerular filtration rates of 25 to 55 ml per minute per 1.73 m^2 of body-surface area. The patients in each diet group will be randomly assigned to a moderate goal for mean arterial pressure (≤107 mmHg) or a low goal (≤92 mmHg) with use of a two-by-two factorial design. In Study B, a diet low in protein and phosphorus will be compared with a diet very low in protein and phosphorus and supplemented with a mixture of essential amino acid and keto acid analogues, in patients with a glomerular filtration rate of 13 to 24 ml per minute per 1.73 m^2. The patients in each diet group will be assigned to a moderate goal for mean arterial pressure of a low goal, as in Study A.

The primary outcome measure of the trial is the rate of change of the glomerular filtration rate. Other outcome measures are the need for dialysis or transplantation, death, the occurrence of serious medical conditions and intercurrent illnesses, nutritional status, blood pressure achieved and compliance with blood pressure regimens, complications related to high or low blood pressure, compliance and satisfaction with dietary regimens, symptoms, the quality of well-being, and the cost of care provided as assessed on the basis of physicians' time, laboratory tests and prescribed supplements.

Acknowledgements

The support of NIDDK grants DK09976 and 5R01DK40321 and the assistance of Ms. Monica White are gratefully acknowledged.

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