REVIEW

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Strategies to prevent progression of renal disease

ABSTRACT

Clinical studies show that several strategies can prevent or slow the progression of renal disease in patients with or without diabetes. This paper reviews current theories of how renal disease develops and progresses and what clinical studies indicate about how to prevent or slow the process.

KEY POINTS

In both diabetic and nondiabetic patients, a clinically proven strategy is to reduce the blood pressure to less than 130/80 mm Hg whenever possible, using an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB), both, or a nondihydropyridine calcium channel blocker as additional therapy or as a substitute for an ACE inhibitor.

Restricting dietary protein to 0.6 to 0.8 g/kg/day is reasonable for both diabetic and nondiabetic patients, if the patient is willing to adhere to a strict diet.

Clinically proven strategies for diabetic patients are to control blood sugar levels to achieve a target hemoglobin A1c level of less than 7% to 8% and to give an ACE inhibitor to any diabetic patient with microalbuminuria, even without hypertension.

PATIENT INFORMATION
Slowing the damage of kidney disease, page 152

OUR THINKING about how renal disease develops and progresses has changed in recent years. Previously, we believed that the kidney received a continuous injury—a situation that in fact occurs in polycystic renal disease and severe lupus nephritis. Now, however, we know that progressive renal disease more often is due to the combination of an initial injury and a maladaptive response to that injury, a response that involves the release of cytokines and vasoactive hormones. These factors seem to be at work in kidney disease caused by hypertension, diabetes, and various types of idiopathic glomerulonephritis.

This paper outlines some of the mechanisms responsible for progressive renal disease, reviews the clinically proven treatments that slow the progression of diabetic and nondiabetic nephropathy, and introduces experimental data that provide insight into future therapies for progressive nephropathy.

RETHINKING HOW RENAL DISEASE PROGRESSES

FIGURE 1 depicts intrarenal factors known to contribute to progressive renal injury.

Most renal diseases cause an initial injury that results in a loss of functioning nephrons. Each remaining nephron therefore has to work harder, filtering more blood per minute to maintain homeostasis. To do this, the kidney secretes intrarenal vasoactive hormones such as prostaglandin E_2 that preferentially dilate afferent arterioles (ie, the arterioles leading into each glomerulus) and other hormones such as angiotensin and catecholamines that constrict efferent arterioles (ie, those leading out of the glomerulus).

TABLE 1

Strategies for preventing or slowing the progression of renal disease

Proven benefit

Aggressive blood pressure control
Goal: < 130/80 mm Hg
Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and nondihydropyridine calcium antagonists preferred

For patients with diabetes:
Tight glycemic control
ACE inhibitors (even if normotensive)
Angiotensin receptor blockers

Possible benefit

Dietary protein restriction
Lipid-lowering therapy with statins
Control of hyperuricemia

Following a low-protein diet for 9 years may delay dialysis by 1 year

Each glomerulus therefore receives more blood at a higher pressure, and therefore filters more fluid into tubules—too much for its own good. This situation, called hyperfiltration, damages the glomerular capillary in subtle ways and stimulates release of cytokines such as transforming growth factor-beta$_1$ (TGF-beta$_1$). All of this can produce further relentless injury and scarring of the remaining nephrons.

In addition, most renal diseases are accompanied by systemic hypertension and proteinuria, both of which are thought to contribute to this ongoing maladaptive intrarenal response.

Diabetic renal disease, on the other hand, begins not with loss of nephrons, but rather with glomerular hyperfiltration and cytokine stimulation, and then progresses to nephron loss and glomerular sclerosis.

The growing knowledge of how these factors contribute to progressive renal disease led to several clinical studies that tested interventions to prevent renal disease or slow the rate of progression of renal disease (TABLE 1).

DIETARY PROTEIN RESTRICTION: POSSIBLY BENEFICIAL, BUT DIFFICULT

Extensive studies of chronic renal failure in animals showed that reducing protein in the diet reduces glomerular hyperfiltration and slows the progression of renal disease. But do these results apply to humans? To date, more than 35 human studies in nondiabetic renal disease and more than 15 studies in diabetic renal disease have been conducted to find out.[1]

The Modification of Diet in Renal Disease (MDRD) study[2] was the largest of these studies. Patients with impaired renal function (a glomerular filtration rate [GFR] of 25–55 mL/min/1.73 m^2) but without diabetes requiring insulin were randomly assigned to follow one of three diets: usual (1.3 g/kg/day), low-protein (0.6 g/kg/day), or very-low protein (0.28 g/kg/day). At the same time, they received antihypertensive treatment with two different blood pressure goals (more about this later).

For protein restriction, the results were inconclusive: at 2.2 years, GFRs had fallen by about the same amount with all three diets.

Not everyone accepts this conclusion, however. For example, Beck et al[3] reanalyzed the MDRD data and concluded that a prescribed dietary protein intake of 0.6 g/kg/day reduced the rate of progression by about 28%, the same benefit as with the low blood pressure goal.[3] A meta-analysis[1] of five of the best studies of both diabetic and nondiabetic renal disease suggested that dietary protein restriction reduces the rate of progression slightly. In another analysis of the MDRD data, Locatelli and Del Vecchio[4] calculated that following a low-protein diet for 9 years would delay the need for dialysis by approximately 1 year.

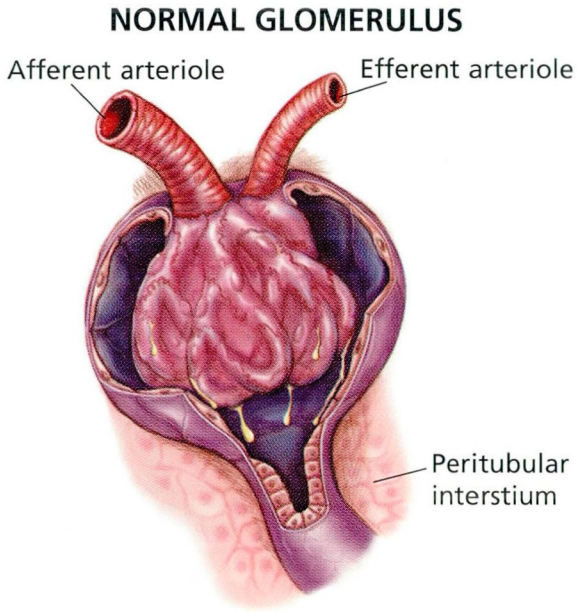
Low-protein diets are hard to follow, however, especially for people with diabetes, making this intervention unwieldy and prone to failure. Patients in the MDRD study met regularly with dietitians for intensive education, and even so, those in the low-protein group, who were supposed to consume no more than 0.6 g/kg/day, managed to lower their intake to only 0.7 to 0.75 g/kg/day. They did not, however, suffer any adverse nutritional outcomes.

CONTROL OF HYPERCHOLESTEROLEMIA: NOT PROVEN BENEFICIAL

Studies in animals suggested that lipid-lowering agents (specifically, statins) favorably affect several processes known to be part of

How renal disease develops and progresses

Most renal diseases progress as the result of ongoing, linked processes that progressively reduce the number of functioning nephrons; interrupting these processes may prevent or slow the damage.



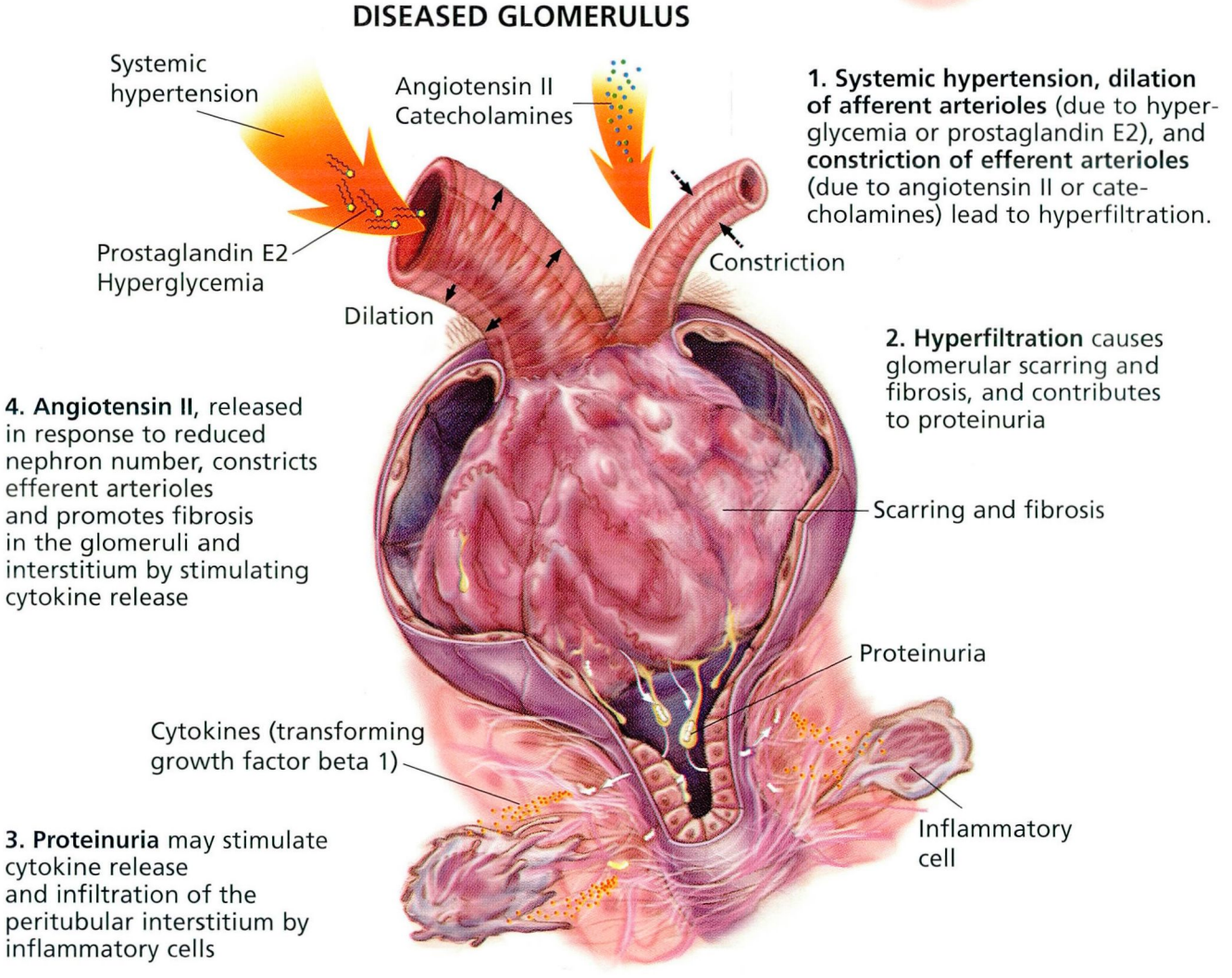


FIGURE 1

progressive nephropathy,[5] inhibiting the proliferation of mesangial cells, vascular smooth muscle cells, and tubular epithelial cells in response to various mitogenic stimuli and reducing the release of cytokines from macrophages. In addition, these agents slowed the rate of progression of renal disease in rats that had 1 5/6 kidneys removed (a model that simulates the loss of nephrons from other causes).

However, to date, no clinical trial has been conducted in humans to show whether lipid-lowering slows the progression of renal disease. In many patients with renal disease, however, lipid-lowering is necessary for other reasons, such as coronary disease or atherosclerosis.

CONTROL OF HYPERURICEMIA: NOT PROVEN BENEFICIAL

Hyperuricemia, hypertension, and renal failure are interrelated. In animals, deposition of uric acid in the kidney causes severe interstitial nephritis, and there is some evidence to suggest that uric acid plays a role in renal disease.[6] But many experts now doubt that hyperuricemia causes chronic renal disease,[7] and no clinical controlled trials have been conducted to assess the value of treating hyperuricemia in preventing renal disease.

ACE inhibitors are more beneficial than expected from their blood-pressure effect

CONTROL OF HYPERTENSION: PROVEN BENEFICIAL

Systemic hypertension is associated with progression of renal disease. The mechanism is partially explained as follows: when diseases cause glomerular injury and loss of nephrons, hyperfiltration in the remaining glomeruli ensues. Hyperfiltration results from afferent arteriolar dilation and efferent arteriolar constriction (FIGURE 1). In this condition the glomerulus receives the full force of the systemic pressure, sustaining further injury.

The MDRD study[2] compared the effect of "usual" blood pressure control (with a goal mean arterial pressure of < 107 mm Hg) vs "low" blood pressure control (with a goal mean arterial pressure of < 92 mm Hg). At 2.2 years, the actual blood pressures in the two groups differed by only 4 mm Hg. Nevertheless, the low blood pressure group had a significantly lower rate of renal failure progression. The benefit was greatest in patients with urinary protein excretion of more than 1 g/day. However, there was no benefit in patients with autosomal polycystic renal disease.

A recent study of 24 patients with autosomal polycystic renal disease[8] compared the effects of the calcium channel blocker amlodipine with those of the angiotensin-converting enzyme (ACE) inhibitor enalapril. During 5 years of follow-up, both drugs reduced blood pressure by a similar amount, but only enalapril was associated with a sustained reduction of urinary albumin excretion. Whether such interventions will translate into improved renal survival in autosomal polycystic renal disease remains to be proven.

Two studies[9,10] included more than 700 nondiabetic patients with renal disease and showed that lowering systemic blood pressure with ACE inhibitors or a sustained-release form of the calcium channel blocker nifedipine reduced the rate of progression of renal failure—especially in patients with proteinuria of more than 1 g/day.

The Ramipril Efficacy in Nephropathy (REIN)[11] trial followed 356 patients with proteinuria of more than 1 g/24 hours, randomized to ramipril or placebo plus conventional antihypertensive medications to lower the diastolic blood pressure to less than 90 mm Hg. After a median follow-up of 31 months at similar levels of blood pressure reduction, the ACE inhibitor was more effective in preserving renal function. This effect was greatest in patients with the highest baseline levels of proteinuria.

Together, these results support the belief that reducing systemic hypertension slows or prevents progression of proteinuric renal disease. They also show that ACE inhibitors prevent progression of renal disease not only by reducing systemic blood pressure, but also by direct intrarenal effects. These intrarenal effects include a favorable change in glomerular hemodynamics (ie, dilating efferent arterioles) and a reduction of angiotensin-mediated fibrosis.

PREVENTING AND CONTROLLING DIABETIC KIDNEY DISEASE

Patients with type 1 (insulin-dependent) and type 2 (non–insulin-dependent) diabetes often develop glomerular hyperfiltration before any clinical evidence of proteinuria or kidney disease arises. Further, studies in diabetic rats showed diabetic nephropathy can be prevented or mitigated by reducing glomerular hyperfiltration by interrupting the angiotensin effect in the kidney, controlling blood pressure, and carefully controlling blood sugar levels.

Several clinical studies in humans showed that the following interventions significantly affect the course of diabetic renal disease.

Tight glycemic control. In the Diabetes Control and Complications Trial (DCCT),[12] tight vs usual glycemic control in type 1 diabetic patients significantly reduced microalbuminuria and the likelihood that microalbuminuria would transform into overt nephropathy.

ACE inhibitors. Lewis et al[13] compared the effects of captopril and placebo in type 1 diabetic patients with overt diabetic nephropathy. Although the groups had only a small difference in blood pressure at the end of the study, the captopril group had a 50% lower incidence of the combined end points of death, dialysis, and transplantation. This finding suggests that the benefit of ACE inhibition is due to an effect beyond that attributable to blood pressure control alone.

In normotensive patients with type 2 diabetes, normal renal function, and microalbuminuria, Ravid et al[14] showed that ACE inhibition stabilizes serum creatinine levels and prevents overt nephropathy. The same investigators showed that ACE inhibition prevents progression of renal disease in previously untreated type 2 diabetic patients with proteinuria and mild azotemia. Ravid et al,[15] in a study of 156 patients with type 2 diabetes, normal renal function, and no albuminuria, also demonstrated that enalapril treatment was associated with a lower incidence of microalbuminuria, the earliest clinical manifestation of diabetic nephropathy.

Aggressive hypertension control. Lewis et al,[16] in a study of 126 patients with type 1 diabetes, nephropathy, and azotemia, showed that treating blood pressure to a mean arterial pressure of 92 mm Hg vs 107 mm Hg was associated with greater reductions in proteinuria and stabilization of renal function.

Angiotensin receptor blockers. In the first randomized clinical trial comparing an angiotensin receptor blocker (ARB) with an ACE inhibitor, Lacourciere et al[17] showed that the ARB losartan and the ACE inhibitor enalapril equally reduced blood pressure and urinary protein excretion and stabilized renal function in 92 patients with type 2 diabetes and early diabetic nephropathy. This is an important observation because about 10% of patients cannot tolerate ACE inhibitors because of cough, an adverse effect rarely seen with angiotensin receptor blockers.

ROLE OF CYTOKINES IN PROGRESSIVE NEPHROPATHY

The observation that ACE inhibitors reduce renal injury in diabetic and nondiabetic patients, even in the absence of hypertension or proteinuria, raises the question of what other pathophysiologic mechanisms might be at work in progressive renal disease.

In several animal models of progressive renal disease in which tissue fibrosis is a prominent pathologic feature, levels of the cytokine TGF-beta$_1$ are elevated in the renal and systemic circulation.[18,19] Humans with biopsy-proven diabetic renal disease were also found to have very high levels of TGF-beta$_1$.[20] Further, TGF-beta$_1$ mRNA levels were elevated early in diabetic nephropathy and correlated with hemoglobin A_1C levels.[21,22]

Several investigators showed that angiotensin stimulates TGF-beta$_1$ and that suppressing the renin-angiotensin system with ACE inhibitors reduced tissue levels of TGF-beta$_1$.[23,24] These observations imply that ACE inhibitors produce beneficial effects by suppressing TGF-beta$_1$. To investigate this hypothesis, investigators in the Collaborative Study Group Captopril Trial[25] measured serum TGF-beta$_1$ levels at baseline and after 6 months of treatment with either placebo or captopril. At 6 months, TGF-beta$_1$ levels had decreased by 14% in the captopril group but had increased by 11% in the placebo group. In addition, there was an inverse correlation

Monitor protein excretion along with BP, blood glucose, and creatinine

between the change in TGF-beta$_1$ at 6 months and the change in GFR at 2 years, ie, the more the TGF-beta$_1$ declined, the less the GFR declined.

OTHER ANTIHYPERTENSIVE DRUGS

Bakris et al[26] randomly assigned 52 patients with type 2 diabetes, nephropathy, and hypertension to receive one of three types of antihypertensive drugs: a nondihydropyridine calcium channel blocker (verapamil or diltiazem), an ACE inhibitor (lisinopril), or a beta-blocker (atenolol). Each of the three classes of drugs reduced the blood pressure by the same amount, but only the nondihydropyridine calcium channel blockers and the ACE inhibitor reduced both the rate of renal disease progression and the degree of proteinuria. Since reduction of proteinuria in diabetic nephropathy seems to be a marker of benefit, it appears that when an ACE inhibitor cannot be used or must be supplemented, a nondihydropyridine calcium channel blocker is an appropriate addition.

Russo et al[27] compared the short-term effect of an ACE inhibitor and an ARB alone and combined in eight patients with immunoglobulin A nephropathy. Each drug given alone significantly reduced proteinuria, while the two agents together caused a greater reduction in proteinuria than either drug alone.

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PROTEINURIA IN THE PROGRESSION OF RENAL DISEASE

Proteinuria accompanies most progressive renal diseases. In general, the greater the proteinuria, the more likely the disease will progress. Many have considered proteinuria as simply a marker of significant renal injury. Recent studies, however, suggest that the proteinuria itself may contribute to renal injury.[28,29]

Glomerular injury increases the permeability of the glomerular basement membrane, allowing plasma proteins to escape. Some of these proteins are ingested by proximal tubular cells, initiating an inflammatory response that contributes to interstitial scarring. In normal rats with 1 5/6 nephrectomy, Romero et al,[30] Abate et al,[31] and Remuzzi et al[32] showed that lisinopril and mycophenolate significantly reduce proteinuria-induced inflammatory injury. This information suggests that any therapy that reduces proteinuria may have a benefit beyond that seen with blood pressure reduction or alteration of glomerular hemodynamics.

In view of these observations, treatments to prevent the progression of renal disease should be monitored not only by measuring blood pressure, blood glucose, and serum creatinine, but also by measuring the effect of such treatment on the degree of proteinuria.

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