The Role of Hypertension in Progression of Chronic Renal Disease

Two patient groups in the study of diet in renal disease. The Modification of Diet in Renal Disease (MDRD) study involved two patient groups. The group in which patients had moderate renal dysfunction (glomerular filtration rate [GFR] between 25 and 55 mL/min) was called Study 1. The other group, which included patients who had more severe renal dysfunction (with a GFR between 13 and 24 mL/min) was called Study 2. The effects of the lower blood pressure (BP) target on patients with proteinuria in Studies 1 and 2 are shown. The y-axis divides patients in Studies 1 and 2 into three groups, depending on urinary protein excretion. The x-axis represents the rate of GFR decline. In the subset of patients in the MDRD trial in both Studies 1 and 2 who had massive proteinuria (protein over 3 g/24 h), the lower blood pressure had an especially salutary effect: the decline in GFR was much slower [37].

FIGURE 6-27

Proteinuria as a marker for progressive renal disease. Nephrotic proteinuria may be a more important and independent marker for progression of renal disease than is hypertension. That is, patients in whom massive proteinuria and hypertension coexist have the worst renal prognosis. In a study of over 400 patients with renal insufficiency followed over 2 years, Locatelli and coworkers [38] found that patients who had both a mean blood pressure (BP) higher than 107 mm Hg and protein excretion of 1 to 3 g/24 h had the lowest rates of renal survival.

FIGURE 6-28

The effect of reduction of proteinuria on the stabilization of renal function. The observations that the potentially correctable factors of hypertension and proteinuria predict the decline of renal function lead to the hypothesis that antihypertensive agents in the angiotensin-converting enzyme (ACE) inhibitor class may be especially important in treatment of hypertension in renal disease. Praga and coworkers [39] investigated 46 patients with nondiabetic renal disease and massive proteinuria treated with the ACE inhibitor captopril. These authors found that proteinuria was decreased by about half. In patients with the greatest reduction in proteinuria (group A), a greater stabilization of renal function occurred over time when compared with those (group B) whose reduction in proteinuria was less.
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**FIGURE 6-30**
Large study of patients with diabetes mellitus and renal disease randomly assigned to captopril or placebo. Lewis and coworkers [40] have studied the use of the angiotensin-converting enzyme inhibitor captopril in patients with type I diabetes mellitus who have diabetic nephropathy and proteinuria. Captopril provides strong protection against progression of renal disease. Those patients treated with captopril had a significant decrease in proteinuria and a slower rate of disease progression, as defined by the time to doubling of the serum creatinine, as compared with patients randomized to placebo.

**FIGURE 6-31**
Study of patients with renal disease not associated with diabetes randomly assigned to ramipril or placebo. A study structured similarly to that in Figure 6-30 examined the use of the angiotensin-converting enzyme inhibitor ramipril in over 150 patients with nondiabetic renal disease [41]. The primary conclusion of the study is summarized. Blood pressure and proteinuria decreased more significantly in the patients treated with ramipril. This group had significantly lower rates of decline in glomerular filtration rate (GFR) over time. This effect was increasingly striking as the baseline level of proteinuria increased and was most pronounced in patients with a urinary protein excretion of over 7 g per 24 hours.

**FIGURE 6-32**
Meta-analysis of over 1500 patients with renal insufficiency. A recent meta-analysis examined randomized studies comparing an angiotensin-converting enzyme inhibitor (ACE) to other antihypertensive agents [42]. None of the individual studies showed that the relative risk for development of end-stage renal disease (ESRD) was statistically lower in patients treated with ACE inhibitors. The pooled relative risk, incorporating data from all the studies, however, was lower in the cohort groups treated with ACE inhibitors.
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**FIGURE 6-33**
Calcium channel blockers. Calcium channel blockers are prescribed widely to patients with normal renal function and affect renal protein excretion variably. The general consensus is that the non-dihydropyridine calcium channel blockers diltiazem and verapamil decrease proteinuria, whereas the dihydropyridine agents have minimal or minor effects on proteinuria.

**FIGURE 6-34**
The effect of calcium channel blockers on preservation of renal function. Most studies of angiotensin-converting enzyme (ACE) inhibitors versus other agents did not examine calcium channel blockers. In a paper by Zucchelli and coworkers [43], patients with nondiabetic renal diseases and hypertension initially were treated with adrenergic antagonists, diuretics, and vasodilators. These patients were then randomized to treatment with the dihydropyridine calcium entry antagonist nifedipine or to the ACE inhibitor enalapril. The rate of decline in renal function was most rapid in the pre-randomization phase in patients treated with conventional antihypertensive agents, mostly adrenergic antagonists. The rate of decline then slowed after randomization. No significant difference in rates of decline was seen in patients treated with nifedipine compared with those treated with captopril. (From Zucchelli and coworkers [43]; with permission.)

**FIGURE 6-35**
The effect of angiotensin-converting enzyme inhibitors and other antihypertensive agents on stabilization of renal function in non-insulin-dependent diabetes. Bakris and coworkers [52] studied patients with non-insulin-dependent diabetes mellitus, hypertension, proteinuria, and presumed diabetic nephropathy. These patients were randomized to treatment with the angiotensin-converting enzyme inhibitor lisinopril; the beta-blocker atenolol; or a nondihydropyridine calcium channel blocker (NDCCB), either verapamil or diltiazem. The primary conclusion of the study is summarized. The change in glomerular filtration rate as a function of time is depicted in groups of patients receiving lisinopril, calcium channel blockers, or atenolol. The creatinine clearance rate declined in all three groups. However, the slope of the decline was significantly greater in the group treated with atenolol and not significantly different between the groups treated with lisinopril and the calcium entry antagonist.