Prevention of the Development and Progression of Renal Disease

THOMAS H. HOSTETTER
National Kidney Disease Education Program, National Institute of Diabetes and Digestive and Kidney Diseases National Institutes of Health, Bethesda, Maryland.

Abstract. Prevention of the major causes of ESRD, hypertension, and diabetes, is possible. Careful glycemic control can prevent diabetes nephropathy. BP control can likely prevent the large majority of hypertensive renal disease. Testing for diabetic renal disease is well founded. In contrast, screening for hypertensive kidney disease is less well defined. Most established renal disease can be treated with glycemic control in the case of diabetes, BP treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and dietary protein restriction. Other therapeutic targets have been proposed, but are not well established. Future research should focus on defining the high risk patients, developing better markers of risk, and designing additional therapies.

Prevention of renal disease is, in principle, possible for the major causes. Indeed, for the largest single cause of kidney failure in the United States, type 2 diabetes, prevention of the diabetes itself is possible. On the other hand, a number of renal diseases are not yet preventable. For example, the major Mendelian inherited diseases and the principal glomerulonephritides cannot be prevented. In practice, most renal diseases including the major categories of diabetes and hypertension are detected at some stage after substantial renal injury. In these cases, available therapies can slow progression to ESRD in many patients and may prevent progression in some. The relatively recent identification of these effective therapies provides the rationale for testing patients who are at risk for kidney disease. This review will consider prevention of renal disease, tests for kidney disease, therapies available to slow progression of CKD, the value of treating it, and some future needs.

Type 2 diabetes is the biggest single cause of ESRD in the United States (1). Moreover, diabetic nephropathy due to type 2 diabetes constitutes the major reason that the incidence of ESRD is rising in the United States. Recent studies from Finland and the United States have demonstrated that people at risk for developing type 2 diabetes can reduce that risk lifestyle changes and drugs (2,3). At present, it is impossible to prevent type 1 diabetes. Although lifestyle and diet have major influences on the level of hypertension, a program of primary prevention of hypertension has not been implemented in the United States. In type I diabetes, the Diabetes Control and Complications Trial (DCCT) provided the evidence that assiduous blood sugar control reduces the appearance of kidney damage (4). Although the trial did not follow patients to demonstrate reductions in ESRD, or even decline in GFR, it did show that intensive glucose control reduced the incidence of microalbuminuria. This effect has persisted, even after the conclusion of the trial although hemoglobin A1c levels have risen somewhat in the initially intensively treated group. Although somewhat less conclusive, the United Kingdom Prospective Diabetes Study (UKPDS) of type 2 diabetes confirms that glycemic control in this much larger patient population can mitigate the development of renal disease (5).

Hypertension is the second leading cause of ESRD in the United States. Observational studies suggest that higher levels of BP predict greater development of renal disease. In a very large cohort of men, a significant increase in relative risk for ESRD was noted even with high normal pressure defined as 130 to 139/<90 mmHg or >140/85 to 89 mmHg (6). Thus, it seems likely that attention to standard guidelines for primary hypertension while maintaining BP at less than 140/90, if applied early in the diagnosis of hypertension, would reduce but perhaps not eliminate ESRD as a complication of chronic hypertension.

The exact segments of the population who would be most fruitfully screened for kidney injury have not been defined in a rigorous manner. Current guidelines support testing patients with diabetes for the presence of albuminuria (7). These guidelines in general suggest testing people with type I diabetes after at least 5 yr and then yearly thereafter. Patients with type 2 diabetes are advised to have testing for albuminuria at the first diagnosis of their disease and yearly thereafter. These guidelines are sensible because 20% to 30% of people with diabetes eventually suffer from ESRD. Because the number of people with hypertension is three- to fourfold larger than those with diabetes, and the number who progress to ESRD is about half that of diabetes, screening is more expensive. Regular screen-
ing on the order of that suggested for diabetes has not been a widely promulgated guideline. However, specific therapy is suggested for hypertensive patients who develop renal injury. Thus, even if no formal evaluation is performed, some level of testing seems reasonable. Periodic, perhaps every 3 yr so long as the test remains normal, measurement of serum creatinine and a test for macroalbuminuria by standard dipstick methodology may be appropriate. In the African American Study of Kidney Disease (AASK), very low levels of proteinuria were predictive of progression, further supporting the regular testing for microalbuminuria (8). Testing for patients who have relatives with ESRD has been suggested. In the cases associated with simple Mendelian traits, such as polycystic kidney disease and Alport’s syndrome, this seems reasonable and might include tests as extensive as imaging and biopsy studies. However, among relatives of patients who have developed ESRD due to hypertensive or diabetic nephropathies, the degree and frequency of testing are uncertain. At minimum, these individuals should be screened for diabetes and hypertension themselves.

For most types of renal disease, progression of established disease can be significantly attenuated. Three principal areas of therapy have proven efficacy. Glycemic control attenuates further injury in patients with diabetes. Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) use blunts renal functional decay in most types of disease. Finally, reductions in dietary protein intake reduce CKD progression across several disease categories.

The DCCT trial demonstrated that even in patients who had microalbuminuria, the risk for developing greater degrees of proteinuria was diminished by intensive blood sugar control (4). In the UKPDS trial, in patients with type 2 diabetes, markers of kidney damage including microalbuminuria, proteinuria, and elevation in serum creatinine were all attenuated by blood glucose control using any of several regimens (5). These observations in both type I and type 2 diabetes accord with the many observational and basic studies demonstrating that glucose control can not only prevent the earliest evidence of diabetes, but can also retard the course of established diabetic injury. Furthermore, glucose control reduces other complications of diabetes. The patient who has microalbuminuria, macroalbuminuria, or even reduced renal function is likely to benefit from careful attention to blood sugar.

The interruption of the renal-angiotensin-aldosterone system, most commonly achieved by ACE inhibitors, reduces progression of renal disease across a wide spectrum of diseases (9). The first demonstration of this effect in large-scale clinical trials was in patients with type I diabetes with moderately reduced renal function and macroalbuminuria, performed more than 10 yr ago (10). Since then, the value of ACE inhibitors as therapy to slow progression has been demonstrated in patients with nondiabetic forms of renal disease. A recent examination of the individual data in a meta-analysis design by Levey and co-workers further substantiated the value of these drugs in this setting (11). More recently, ARB have become available and studies using these agents have demonstrated the same generally salutary effects in nephropathy due to type 2 diabetes. Indeed, diabetic patients with early microalbuminuria and normal GFR displayed reduction in their risk of transition to high-grade proteinuria with the institution of ARB (12). This result is reminiscent of smaller studies using ACE inhibitors in both type 1 and 2 patients with microalbuminuria, even without arterial hypertension. Patients with more advanced kidney damage due to type 2 diabetes had reductions in their progression to more serious disease including dialysis (13,14). The AASK tested ACE inhibitors versus calcium channel blockers and beta-blockers in African Americans with hypertension-induced renal insufficiency (8). As in diabetes and other progressive renal diseases, ACE inhibitors proved superior in modifying the course of kidney injury. Thus, firm evidence has accumulated for ACE inhibitors and to a lesser extent ARB in reducing progression in renal disease. At present the only major category of kidney disease for which doubt exists about the preferential effectiveness of ACE inhibitors is polycystic kidney disease.

The level of BP targets for the patient with kidney disease is far less well established than the merit of an ACE- or ARB-based regimen. Current guidelines in the United States call for lower BP than 130/80 in people with kidney disease (7,15,16). The exact targets are unclear and the evidence for this is modest.

The third major category of intervention for those with kidney injury is the reduction of dietary protein intake (17). In many ways this is the most clinically cumbersome approach to attacking progressive renal disease. Nevertheless, meta-analyses have consistently confirmed the value of dietary protein restriction as a maneuver for reducing progressive kidney injury across a relatively wide range of disease categories.

The consistently beneficial effects of renin-angiotensin-aldosterone system blockade have focused attention on further refinement and exploitation of this therapeutic strategy. The combination of ACE inhibitors and ARB has been examined through a number of largely short-term or small studies (18,19). These results are to date inconclusive, but recent comparison of combination and monotherapy suggested additional therapeutic advantage for the combination (19). The addition of a specific blocker for aldosterone action is beginning to be studied with the reservation that serious hyperkalemia may follow such therapy in patients already on ACE inhibitors. Nevertheless, encouraging results have appeared from preliminary or very small studies (20).

A number of more specific metabolic targets in the cascade of hyperglycemic-induced damage have been identified for treatment of diabetic complications. These include inhibitors of advanced glycosylated end-product (AGE) formation or interaction with its receptors, protein kinase C inhibitors, aldose reductase inhibitors, and other metabolic inhibitors. However, these approaches to interrupting the distal complications of hyperglycemia have not been established as valuable therapies in diabetic renal disease.

A large variety of potentially modifiable factors that either occur with progressive renal disease, or are thought to accelerate it, have been proposed as therapeutic targets. These include smoking cessation, lipid lowering, homocysteine treat-
ment, anemia therapy, calcium/phosphorus and parathyroid hormone-directed manipulations, attenuation of acidosis, and reductions in dietary salt intake. Although each of these modalities has some rationale in epidemiologic and/or experimental studies, large-scale clinical trials have not been done to test their benefit. However, several of them, such as smoking cessation and cholesterol-lowering, are so critical to reducing the now apparent cardiovascular risk that is associated with renal insufficiency, that their value can hardly be questioned (21). The renal benefits may remain uncertain.

An increasing body of literature supports the economic value of early detection and treatment of chronic renal disease (22,23). Most of these analyses have revolved around reductions in the economic costs of ESRD. Reductions in disability and suffering, although in principle quantifiable to some degree, have been less examined. As one would predict, the earlier the renal disease is detected, the longer effective therapy can provide dialysis-free survival (24). In addition, there would be an associated reduction in dialysis and transplantation expenses and disabilities. Treatment is likely to reduce cardiovascular disease in patients with renal insufficiency. Although formal studies are lacking, the burgeoning evidence that CKD and proteinuria are independent risk factors for cardiovascular disease suggests that not only reductions in ESRD, but reductions in death and morbidity due to cardiovascular events would follow from therapy with more intensive glycemic and BP management (21). Finally, declines in the very high rate of cardiovascular disease in patients who have progressed to ESRD might be anticipated if ACE inhibitors were consistently applied during their renal disease. Patients who develop kidney failure have a 5- to 100-fold increased risk of cardiovascular death compared with the non-ESRD population. Efforts applied before ESRD might reap the benefits in reducing this injury even if the ESRD itself were not completely averted.

Although the range of patients who may benefit from ACE inhibitor or ARB therapy may be wide, the above discussion has focused on applying these therapies to patients with established, even if apparently mild, renal disease, like the normoalbuminuric diabetic. That is, the treatment pathway would only begin with detection of renal disease. At least one study, however, has argued that institution of ACE inhibitor therapy in all type 2 diabetics above 55 yr of age would be beneficial (24). No existing guidelines, to my knowledge, have followed this conclusion. Nevertheless, the idea is intriguing. Such a practice would reduce the cost for screening and detection, and by removing the need to interpret tests might make application of this therapy more widespread. Further analyses of the treatment of subjects who are merely susceptible to progressive renal disease, even before evidence of renal disease exists, is awaited. One prospective trial of normoalbuminuric type 1 diabetics is in progress.

Several research needs can be identified from the above considerations. First, more accurate prediction of subjects at risk would be beneficial. In this regard, genetic definition of risk and more sensitive and easily applied measures for testing for renal disease are needed. These tools could include approaches as simple as reporting estimated GFR, along with accurately measured serum creatinine or other newer markers of GFR such as cystatin. Cytokines or other biomarkers measurable in urine or even anonymous proteomic approaches to identifying patients at risk for renal disease can be envisioned as risk predictors and even markers for effective treatment. Combinations of these newer laboratory approaches with epidemiologic study could more precisely target individuals in whom screening is most effective. Analyses of screening approaches in hypertension would be of substantial value. In addition to detection of renal disease, better therapies are clearly needed. Current available therapies, although effective, are imperfect, and further efforts to develop simple therapies to slow progression and ultimately prevent the progression of renal disease are yet another research need.

References


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