Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the United States, and accounts for 35% of all the patients with ESRD entering a dialysis program; 63% of patients with diabetic nephropathy have type II diabetes mellitus. Hypertension is a major risk factor for renal disease and is common in people with diabetes mellitus. Strategies for preventing the progression of renal failure in patients with diabetes mellitus include glycemic control, and control of blood pressure. Blocking the renin-angiotensin system (RAS) slows the progression of established diabetic nephropathy in type I diabetes mellitus, and inhibiting angiotensin II formation retards or impedes the progression from microalbuminuria to established diabetic nephropathy (macroproteinuria) in people with type I diabetes mellitus. The situation could be the same for people with type II diabetes mellitus. The ability of RAS blockade using irbesartan, an AT1 angiotensin II receptor antagonist, to slow the progression in renal failure has been compared with that of the calcium channel blocker amlodipine and placebo in a pilot study. The results suggest that blockade of the RAS, in this case with irbesartan, is at least equivalent to calcium channel blockers with respect to antihypertensive efficacy, but provides better renoprotective benefits. Am J Hypertens 1997; 10:325S–331S © 1997 American Journal of Hypertension, Ltd.

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diabetic nephropathy has substantial long term health and economic benefits.

Devising strategies aimed at preventing or delaying the development of diabetic nephropathy requires a thorough understanding of both the causes of renal dysfunction and the role that diabetes plays in the development of renal disease. The objective of this article is to provide an overview of the causes and processes that lead to a diabetic nephropathy and to review recent evidence supporting the renoprotective effect of blocking the renin-angiotensin system (RAS).

FACTORS CONTRIBUTING TO THE DEVELOPMENT OF RENAL DISEASE IN PATIENTS WITH DIABETES MELLITUS

Numerous factors predispose individuals with diabetes to development of renal disease. Generally, these factors are similar for both type I and II diabetes mellitus. Hypertension is a major risk factor and is common in people with diabetes. Race is also an important predisposing factor: Australian aborigines, Polynesians and Maori, black Americans, Hispanics, and Native Americans, particularly the Pima Indians, with type II diabetes mellitus are at a higher risk for development of ESRD compared with whites with diabetes. Other risk factors include duration of diabetes mellitus, gender (black men with type II diabetes mellitus are at greater risk than black women with type II diabetes mellitus), family history of kidney disease, smoking, and hyperglycemia.

The risk of developing renal damage in patients with both type I and type II diabetes mellitus is substantial, but not all persons with these disorders develop renal damage. Furthermore, in type II diabetes mellitus, renal damage does not depend on the presence of diabetic nephropathy in a small but significant percentage of cases. The percentage of nephropathies that are not associated with diabetes mellitus is higher in persons with type II diabetes mellitus compared with that in persons with type I diabetes mellitus. Therefore, a renal biopsy could be needed in patients with type II diabetes mellitus and renal dysfunction to confirm the diagnosis of diabetic nephropathy. However, based on the actual knowledge of the pathophysiology of renal disease, with the possible exception of polycystic kidney disease, nondiabetic primary renal disease should be treated the same as diabetic nephropathy in order to halt the progression of chronic renal failure. Blockade of the RAS and blood pressure control are the two most relevant factors.

THE NATURAL HISTORY OF DIABETIC NEPHROPATHY

As mentioned previously, the prevalence of diabetic nephropathy in persons with type II diabetes mellitus is increasing. One likely reason for this increased prevalence is that the mortality rate due to cardiovascular disease is decreasing. Consequently, we have the opportunity to observe the development of chronic renal failure in type II diabetics, who some years ago would have died as a result of cardiovascular disease. In other words, we now can observe the natural history of nephropathy in type II diabetes mellitus.

Figure 2 summarizes the natural history of type II diabetic nephropathy, which is similar to that of individuals with type I diabetes mellitus. Following the onset of diabetes mellitus, the first functional changes indicating the presence of diabetic nephropathy are alterations in renal hemodynamics, including renal vasodilation and reduced renovascular resistance, with consequent increases in renal plasma flow (RPF) and glomerular filtration rate (GFR). Another early functional change is increased urinary albumin excretion (microalbuminuria), which may be correlated with elevated GFR, and which often progresses in 5 to 10 years to macroalbuminuria. Microalbuminuria is present in approximately 25% to 30% of patients with type II diabetes mellitus.

A number of histologic and morphologic changes are also associated with diabetes mellitus, including renal hypertrophy, glomerular basement membrane thickening, mesangial expansion, diffuse or nodular glomerulosclerosis, and arteriolar hyperplasia and hyalinosis. These structural changes appear to develop in parallel with, or may precede, changes in renal function, but the exact relationship between structural and functional changes is not fully understood.

In addition to being an early sign of renal dysfunction, microalbuminuria is an important predictor for cardiovascular disease and is a major risk factor for death in persons with diabetes mellitus. The risk of death from cardiovascular disease in patients with microalbuminuria is approximately three times that for nondiabetic individuals. Moreover, individuals with type II diabetes mellitus and microalbuminuria...
have an increased risk of myocardial infarction and stroke before they develop chronic renal failure. Microalbuminuria progresses to proteinuria in 22% to 50% of patients within 5 to 10 years. Once proteinuria has developed, there is a progressive decrease in GFR of approximately 4 to 12 mL/min/year, which leads ultimately to ESRD in many cases.

Factors that enhance the rate of decline in renal function include smoking, an increased serum lipid concentration, and arterial hypertension. It has been difficult to establish a causal relationship between the development of hypertension and that of renal dysfunction. For example, an increase in blood pressure (BP) usually follows the appearance of microalbuminuria by 2 to 5 years in individuals with type I diabetes mellitus. In contrast, hypertension often precedes the development of microalbuminuria in individuals with type II diabetes mellitus. In either case, however, hypertension is a strong indicator that renal function will progressively decline unless corrective measures are taken.

Strategies for preventing the progression of renal failure in patients with diabetes mellitus include glycemic control and control of BP. Cessation of smoking, lipid lowering therapy, and a low protein diet are also important preventive steps.

THE ROLE OF HYPERTENSION IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY

The benefits of BP control on the rate of progression of renal disease in people with type I diabetes mellitus have been demonstrated in a number of studies. Fewer studies have examined the relevance of BP control in people with type II diabetes mellitus, but results suggest that control of BP is associated with renoprotective benefits in people with type II disease as well. The rate of decline in renal function is highly dependent on BP, and there is a direct correlation between mean BP and the decay in renal function as determined by percent change in the reciprocal of serum creatinine level. For example, one study reported that the percent decrease in renal function is 6% and 13.5%/year in patients with types I and II diabetes mellitus, respectively, when systolic BP is >140 mm Hg, compared with <1% for both types I and II diabetes mellitus when systolic BP is ≤140 mm Hg. These results suggest that there are substantial benefits to be gained from lowering BP at least to 140/90 mm Hg. Recent data suggest, however, that the traditional target BP of 140/90 mm Hg for patients with renal dysfunction may be too conservative, and that a greater degree of renoprotection can be achieved when BP is maintained at <140/90 mm Hg.

The effect of blocking the RAS in delaying or preventing the progression from incipient nephropathy (characterized by microalbuminuria) to overt nephropathy (characterized by proteinuria) and renal failure are now widely recognized, thanks to the studies performed with ACE inhibitors. On the other hand, it remains to be known whether some classes of antihypertensive agents offer better renoprotection for a similar degree of BP control than do other classes. Calcium channel blockers (CCB) are frequently used to treat hypertensive patients with diabetes mellitus. There has been some debate, however, concerning their ability to slow the progression of renal failure. For example, there have been reports that the dihydropyridines could accelerate the loss of renal function in animal models of renal disease and diabetes. This effect may result from the ability of some CCB to preferentially dilate preglomerular vessels, leading to glomerular hypertension. Results of studies in humans are inconsistent, but some evidence suggests that the dihydropyridine CCB, such as nifedipine and amlodipine, provide a degree of renoprotective benefit. Other researchers have reported that diltiazem...
and verapamil decreases urinary protein excretion without exacerbating preexisting renal dysfunction, whereas nifedipine increases urinary protein excretion and worsens preexisting renal dysfunction. Thus, a full understanding of the effect of CCB on renal function requires further studies.

**ROLE OF THE RENIN-ANGIOTENSIN SYSTEM IN RENAL FUNCTION**

 Interruption of the RAS lowers systemic BP by inhibiting the pressor effect of angiotensin II (AII). Blockade of the RAS has several advantages with respect to renal function. AII is a potent vasoconstrictor and is also implicated in the progression of renal failure in diabetic nephropathy. Inhibition of the RAS causes a dilation of arteries and a decrease in systemic BP. In the kidney, decreased efferent arteriolar resistance lowers intraglomerular pressure, resulting in a decrease in albumin excretion rate, which helps to slow progression of chronic renal failure. In addition to mediating the abnormal hemodynamic response at the glomerular level, AII alters matrix metabolism by promoting inflammation and fibrosis, thus contributing to histopathologic changes observed in many patients with renal impairment.

 Inhibition of AII with ACE inhibitors or AII receptor antagonist (AIIRA) could arrest the sequence of events leading to ESRD by decreasing efferent arteriolar resistance and by blocking the other effects of AII. In this respect, interruption of the RAS with ACE inhibitors has been proven to be beneficial for hypertensive as well as for normotensive patients with diabetes.

 The renoprotective benefits of ACE inhibitors have been demonstrated in patients with type I diabetes and overt diabetic nephropathy, and some evidence suggests that they are renoprotective in type II diabetes as well. Results of clinical trials have demonstrated that ACE inhibitors lower proteinuria independent of BP control alone. Thus, it appears that blockade of the RAS is a promising approach to slowing the development of diabetic nephropathy even in normotensive individuals. However, use of ACE inhibitors could be contraindicated in patients with renal artery stenosis due to the fact that renal function could decay after ACE inhibition. Additionally, there is an increased risk of hyperkalemia, which could be more problematic in patients with diabetes.

 **IRBESARTAN IN THE TREATMENT OF PROGRESSIVE RENAL FAILURE**

 Blocking the AII receptor using AIIRA could represent a more targeted approach to inhibiting the RAS than using ACE inhibitors. AIIRA do not directly interfere with any enzymatic process in the RAS; they simply impede the coupling of angiotensin at the level of the AT$_1$ receptor. In contrast to ACE inhibitors, AIIRA have no direct effect on AII production or bradykinin metabolism. This more targeted mechanism may account for the excellent tolerability profiles observed with the AIIRA.

 Irbesartan (Bristol-Myers Squibb/Sanofi) is a long-acting AIIRA with high selectivity for the AT$_1$ receptor subtype. Irbesartan is rapidly and completely absorbed after oral administration, with an absolute bioavailability > 60%. Maximum plasma concentrations are reached within 2 h, and the plasma half-life of irbesartan is 11 to 15 h. Seventy-five percent of an oral dose of irbesartan is eliminated through hepatic pathways and 20% is eliminated through the renal pathway. As a result of this dual route of elimination, there is no need to adjust the dosage in patients with renal or hepatic impairment. Irbesartan is not removed by hemodialysis and is well tolerated in single and multiple doses up to 900 mg.

 Results of several randomized, double-blind, placebo controlled studies have demonstrated the antihypertensive efficacy and safety of irbesartan in patients with mild-to-moderate or severe hypertension. These studies have shown that irbesartan lowers BP in a dose related manner within 1 week. The antihypertensive efficacy of irbesartan is at least equal to those of the ACE inhibitor enalapril, the CCB amlodipine, and the β-antagonist atenolol. In all studies, irbesartan was extremely well tolerated.

 Several preclinical and clinical studies evaluating the renoprotective benefits of irbesartan have also been performed. In animal models, irbesartan lowers BP and reduces glomerular injury in obese Zucker rats—a widely used experimental model for type II diabetes, characterized by hypertension and renal impairment. In addition, irbesartan decreases urine protein excretion and prevents or slows the development of glomerulosclerosis in fawn-hooded hypertensive rats, suggesting that AII plays an important role in the development of both hypertension and glomerular injury.

 In clinical studies in which irbesartan was administered to normal subjects and to patients with mild-to-moderate renal impairment, severe renal impairment, or on hemodialysis because of renal failure, there was no significant difference between groups in dose normalized irbesartan area under the curve (AUC). In patients with type II diabetes mellitus, irbesartan facilitates renal vasodilation, based on increases in renal blood flow observed after administration. Increased renal blood flow is a result of decreased efferent vascular resistance, ie, dilation of efferent arterioles. These results suggest that irbesartan can confer some renoprotective benefits. More recent studies have examined the renoprotective benefits associated with
Irbesartan in patients with diabetic nephropathy and hypertension.66

IRBESARTAN VERSUS AMLODIPINE

The effects of irbesartan on BP and renal function were compared with those of the CCB amlodipine in a small pilot study in hypertensive patients (seated systolic BP > 135 mm Hg or seated diastolic BP > 85 mm Hg, or both) with type II diabetes mellitus and microalbuminuria, half of whom were black.66 Patients were randomized to double-blind therapy with 75 mg irbesartan once daily or 2.5 mg amlodipine once daily. Doses of the study medication were doubled after 4 weeks and doubled again after 8 weeks, for final irbesartan and amlodipine daily doses of 300 mg and 10 mg, respectively.

The reductions in diastolic BP throughout the 12-week study were similar with irbesartan and amlodipine. Urine protein excretion and creatinine clearance, indicators of renal function, showed that irbesartan provided beneficial renal effects in these patients. After 12 weeks of therapy, irbesartan reduced mean urine protein excretion by 8.5%, whereas amlodipine increased it by 19.7% (Figure 3). There was also a significant difference in the effects of irbesartan and amlodipine on creatinine clearance, with amlodipine decreasing creatinine clearance, compared with baseline and irbesartan slightly increasing creatinine clearance (irbesartan versus amlodipine, $P < .01$). This study showed that irbesartan produced reductions in diastolic BP comparable with those of amlodipine, and also had beneficial renal effects when administered to patients with type II diabetic nephropathy and hypertension.

These results suggest that irbesartan is at least equivalent to the CCB amlodipine with respect to antihypertensive efficacy and that it provides better renoprotective benefits than does amlodipine. Additional studies are necessary, however, to fully explore the long term renoprotective benefits of irbesartan compared with those of amlodipine and other antihypertensive agents.

SUMMARY

Diabetic nephropathy is a leading cause of ESRD worldwide, but steps can be taken to prevent or delay the onset of this disorder, including, among others, controlling BP with antihypertensive agents in patients with diabetes and hypertension. The results of studies of CCB are inconclusive. Some evidence suggests that CCB can provide some degree of renoprotection, whereas other data suggest that at least some CCB could exacerbate renal impairment. Drugs that interrupt the RAS, including ACE inhibitors and AIIRA, have proven renoprotective benefits in animal and human studies. In fact, ACE inhibitors have been shown to postpone the progression of diabetic nephropathy, even in normotensive patients. AIIRA appear to be better tolerated than ACE inhibitors because they do not interfere with any metabolic process in RAS. Thus, AIIRA, such as irbesartan, with its outstanding tolerability profile, represent a promising new therapeutic approach to treating chronic renal failure, particularly in patients with diabetes mellitus.

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