Diabetic nephropathy has become the single largest cause of end-stage renal disease (ESRD) worldwide. Until recently, it was thought that once a patient developed overt proteinuria, diabetic nephropathy was irreversible and inevitably progressed to ESRD. However, the reversal of lesions caused by diabetic nephropathy (e.g., glomerular basement membrane thickening and mesangial matrix increase) has been demonstrated in a series of patients who underwent a pancreas transplantation 10 years prior to the reversal. Remission of nephrotic range proteinuria has also been reported in some patients with type 1 diabetes from the Collaborative Study Group during a median follow-up of 3 years of angiotensin-converting enzyme (ACE) inhibitor administration; no deterioration of renal function was observed in these patients. Remission and regression in nephropathy of type 1 diabetes patients have also been reported when blood pressure was controlled aggressively. Recent clinical trials have demonstrated that angiotensin II receptor blocker (ARB) preserved renal function and slowed the progression of nephropathy to ESRD in patients with type 2 diabetes. Since many patients with type 2 diabetes manifest with a metabolic syndrome, multifactorial intensive treatment is necessary; such treatment includes behavior modifications, dietary intervention, exercise, and smoking cessation. (Hypertens Res 2003; 26: 515–519)

**Key Words:** proteinuria, renin-angiotensin system, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker
characterized by the thickening of the glomerular basement membrane (GBM) and by an increase in the mesangial matrices (5, 6). The thickening of the GBM starts 2 to 5 years after the onset of type 1 diabetes, and becomes obvious after 5 to 10 years (7). The increase in the mesangial matrix leads to mesangial expansion and diabetic glomerulosclerosis (5, 6), which in turn brings about the deterioration of glomerular dysfunction (8). Proximal tubular basement membrane thickening is also an integral component of the morphological changes associated with diabetes; this type of thickening is known to be correlated with GBM width and mesangial expansion (9).

Fioretto et al. (10) performed repeated kidney biopsy after pancreas transplantation in eight patients with type 1 diabetes who had mild to advanced lesions indicative of diabetic nephropathy. The thickness of the glomerular and tubular basement membranes was similar at 5 years, but had decreased by 10 years in comparison with the baseline for these patients (Fig. 1). The mesangial fractional volume (i.e., the proportion of the glomerulus occupied by the mesangium) increased in comparison to the baseline over a period of 5 years, but had decreased at 10 years, mostly because of a reduction in the mesangial matrix (Fig. 1). In this study, a case involving the disappearance of nodular lesions, as well as a reduction of microalbuminuria was presented. These data indicate that the normalization of blood glucose levels can reverse the development of diabetic nephropathy-associated lesions. Furthermore, the importance of long-term glucose level control was emphasized in the study. It was also suggested that the reversibility of glomerulosclerosis may be suggestive of the regenerative nature of the glomerulus.

Blood Pressure Control and Renin-Angiotensin System Blockade

Studies from Animal Models of Diabetes

Many studies have demonstrated the role of the renin-angiotensin system (RAS) in the process of glomerulosclerosis, both in cases of primary glomerulonephritis and in secondary glomerular diseases, most notably in cases of diabetic nephropathy (11–13).

Long-term (70 weeks) administration of angiotensin-converting enzyme (ACE) inhibitor completely prevented the development of diabetic nephropathy in streptozotocin-induced diabetic rats (14). ACE inhibitor limited albuminuria and glomerular injury to values even lower than those in control rats, in spite of continuous hyperglycemia. Although another group that had received reserpine, hydralazine, and hydrochlorothiazide showed comparable blood pressure levels, they exhibited proteinuria and focal glomerulosclerosis. Similar experimental results were obtained by the administration of angiotensin II receptor blocker (ARB) (15, 16). Thus, diabetes in this animal model can completely be prevented by RAS blockade, in spite of continuous hyperglycemia.

Studies of Human Diabetic Nephropathy

Effect of ACE Inhibitor

One of the earliest findings of the benefits of ACE inhibitor was reported by Taguma et al. (17). In this study, a marked reduction of proteinuria was observed in patients manifesting nephrotic syndrome and chronic renal failure after administration of captopril; moreover, this reduction was observed within 2 weeks of the onset of treatment from 10.6 ± 2.2 to 6.1 ± 1.4 g/day. Remission of a nephrotic range of proteinuria levels occurred in 5 of 10 patients. This decrease in proteinuria levels did not coincide with either a fall in systemic blood pressure or a fall in blood glucose, which suggests that a fall in intrarenal hypertension contributed to urinary protein excretion in these cases.

Lewis et al. (18) demonstrated the renoprotective effects of ACE inhibitors for the first time in the Collaborative Study that analyzed the data from a large number of type 1 diabetes patients (207 patients received captopril and 202 received placebo). Captopril treatment was associated with a 50% reduction in the risk of the combined endpoints of death, dialysis, and transplantation; the risk reduction was
independent of a small disparity in blood pressure between the groups. An even more beneficial effect was seen among the patients whose baseline creatinine concentration was > 1.5 mg/dl.

To date, the effects of ACE inhibitors on the progression of type 2 diabetic nephropathy to either the endpoint of ESRD or that of death has not been investigated in a specific, large clinical trial. Longitudinal studies have demonstrated the beneficial effects of ACE inhibitors on stabilizing or reducing proteinuria in patients with type 2 diabetes (19, 20). Although ACE inhibitors are known to stabilize renal function and/or reduce proteinuria, some studies have shown that the ACE inhibitors were in this regard as effective as other antihypertensive drugs (21, 22).

Effect of ARB
A similar renoprotective effect has been reported by ARB in two recently completed randomized clinical trials, namely, an irbesartan diabetic nephropathy trial (IDNT) (23) and a trial considering the endpoint of diabetes in type 2 diabetic patients with the angiotensin-II antagonist losartan (RENAAL) (24). Both studies compared the cardiovascular and renal benefits in ARB treated and placebo patients with type 2 diabetes, who manifested with overt proteinuria and chronic renal failure. ARB was associated with a reduction of the risk of 2-folds increase in the level of serum creatinine; in addition, ARB was associated with a decreased incidence of both the onset of ESRD and death (23, 24). Further study will be necessary in order to identify the subgroups in which remission and regression occur after long-term administration of ARB.

Combination Therapy with ACE Inhibitor and ARB
Combined therapy with ACE inhibitor and ARB may decrease angiotensin II production by inhibiting ACE activity and may also antagonize the effects of chymase-produced angiotensin II by blocking the relevant receptors. Combination therapy proved to be effective at reducing proteinuria in patients with IgA (immunoglobulin A) nephropathy (25) and it was more effective than monotherapy at inhibiting the progression of non-diabetic renal disease (26). This type of combined therapy was superior to either ACE inhibitor or ARB alone at reducing microalbuminuria in patients with type 2 diabetes (27). To determine the effects of combination therapy on glomerular function, further longitudinal studies of more advanced cases of type 2 diabetic nephropathy with established proteinuria will be necessary.

Remission and Regression in Glomerular Diseases

Primary Glomerular Diseases
A Ramipril Efficiency in Nephropathies (REIN) study found that over 36 months of continued ramipril therapy substantially decreased the risk of ESRD in a sample of patients, most of whom had primary glomerular diseases (28, 29). In that continuous REIN study, the effect of ACE inhibitors studied by the GISEN group (30) reported that 10 of 26 patients on continued ramipril therapy had a decreased rate of decline and another 10 patients had an improvement in their glomerular filtration rate (GFR) while on ramipril therapy. The study by the GISEN group was the first report demonstrating the improvement of GFR by ACE inhibitors.

Type 1 Diabetes Mellitus
Remission of nephrotic-range proteinuria was reported by Hebert et al. (31) in the Collaborative Study (18). Of the 409 patients recruited into the study, 108 had a nephrotic range of proteinuria at entry. Remission of nephrotic-range proteinuria occurred in 7 of 42 patients assigned to a protocol of captopril therapy (mean follow-up: 3.4 years) and in 1 of 66 patients assigned to placebo. The remission group did not differ from the group without remission with respect to diastolic blood pressure, glycohemoglobin levels, or cholesterol levels. However, mean systolic blood pressure during the Captopril Study was lower in the remission group than in the no-remission group (126 ± 8 vs. 140 ± 13 mmHg). Hebert et al. (31) concluded that long-term remission of nephrotic-range proteinuria with stable serum creatinine level is a realistic goal for treatment of patients with type 1 diabetes, and they also determined that remission is significantly associated with ACE inhibitor therapy and with achieving a decrease in systolic blood pressure.

Further follow-up care of these 8 patients in remission continued for 7.7 years. Of these patients, 6 stayed in remission; one patient dropped out during the follow-up period, and one patient progressed to ESRD (32). In that study, Wilmer et al. (32) emphasized the importance of blood pressure control and ACE inhibitor therapy in achieving long-term remission.

In a continuous series of the Collaborative Study with ramipril, Lewis et al. (33) found out that a mean arterial blood pressure goal of 92 mmHg or less was associated with a significantly decreased incidence of proteinuria (i.e., from 1,043 mg/day to 535 mg/day). Thirty-two of 126 patients achieved a final total protein excretion of less than 500 mg/day. That study demonstrated that with a combination of ACE inhibition and intensive blood pressure control, many patients were able to achieve remission or apparent remission of diabetic nephropathy.

Hovind et al. (34) aggressively controlled blood pressure in 301 patients with type 1 diabetic nephropathy. They defined remission as albuminuria < 200 µg/min sustained for at least 1 year and at least 30% decrease in albuminuria from the preremission levels (surrogate endpoint). Furthermore, regression was defined as a rate of decline in GFR equal to that of the natural aging process, i.e., ≤1 ml/min/year during
the entire observation period. Ninety-eight (32%) patients achieved a remission of 3.4 years, and 67 (22%) patients achieved regression (Fig. 2). Lower arterial blood pressure, reduced albuminuria, and better glycemic control were predictors of a regression of diabetic nephropathy. These studies suggest that an aggressive blood pressure control goal of a mean arterial blood pressure of 92 mmHg, together with strict glycemic control, can bring about remission and regression of nephropathy in patients with type 1 diabetes.

Type 2 Diabetes Mellitus

Type 2 diabetes should also be considered in this context. In type 1 diabetes, most of patients are young, and the only initial risk factor associated with renal failure is hyperglycemia. On the other hand, many factors such as hypertension, hyperlipidemia, and obesity are associated with the renal lesions in the comparatively older patients with type 2 diabetes. Gaede et al. (35) analyzed the effects of multi-factorial intensive treatment, using a stepwise implementation of behavior modification, pharmacological therapy targeting hyperglycemia, and treatments of hypertension by ACE inhibitors, and dyslipidemia. Patients in the intensive treatment group had significantly lower rates of progression, not only to overt nephropathy, but also to the progression of retinopathy and autonomic neuropathy, than patients in the standard group.

An early study by Taguma et al. (17) most likely included type 2 diabetes; however, the observation period of their study was 8 weeks and was therefore relatively short-term. More recently, Akai and Sato (36) reported the remission of a nephrotic range of proteinuria and a preserved renal function after intensive treatment that included intensive blood pressure control by ACE inhibitors, glucose level control, and a low-protein diet (0.8mg/kg/day). They aimed at achieving HbA1c below 6.5%, possibly 6.0%, by intensive insulin therapy, and at a blood pressure below 130/85 mmHg.

In cases of type 2 diabetes, amelioration of the metabolic syndrome is necessary in order to prevent the development and progression of diabetic nephropathy; such treatment would include intensive RAS blockage.

Conclusions

The first goal of treatment in patients with diabetic nephropathy is remission, i.e., if a nephrotic range of proteinuria is observed, a reduction in urinary protein excretion has to be induced. The second goal is achieving a regression, i.e., the preservation of renal function equal to that of the natural aging process. The third goal is the regression of other vascular complications resulting from diabetes mellitus. To achieve this goal, remission clinics for patients with diabetic nephropathy should be opened. In such clinics, glucose levels would be strictly controlled, as would blood pressure (by ARB/ACE inhibitor). In addition, implementation of behavior modification techniques would be necessary in order to avoid the development of ESRD.

References


