Antihypertensive Treatment and Multifactorial Approach for Renal Protection in Diabetes

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Type 2 diabetes is reaching epidemic proportions throughout the world, representing the most common cause of ESRD. Early identification of renal impairment associated with diabetes and initiation of renoprotective therapy are imperative. High BP, dyslipidemia, long duration of diabetes, and poor glycemic control are important risk factors; their modification, renal function monitoring, and combined therapies are the current integrated approaches to treat patients with diabetic kidney disease. Strong evidence suggests that achieving target BP goals via inhibition of the renin-angiotensin-aldosterone system confers significant renal protection for diabetic patients. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers lower BP and reduce both the progression of renal damage and adverse cardiovascular events; some important renoprotective actions seem to be independent of the antihypertensive effect. Stringent quality of glycemic control is another key point to prevent onset of nephropathy or slow its progression. Evidence from basic research and clinical trials indicates that hypolipidemic drugs, mainly statins, contribute to modulate the progression of renal damage in diabetes; their use should be considered in any patient with diabetes. Smoking cessation may slow nephropathy progression; given the additional health benefits of stopping smoking, this advice is an important part of the strategy of diabetic nephropathy treatment and prevention. In conclusion, a target-driven, long-term, intensified intervention aimed at multiple risk factors should be recommended in patients with diabetes to preserve their kidney function.

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Diabetic nephropathy (DN) is the single most common cause of ESRD in the United States, accounting for >50% of new cases of renal failure. Patients who have diabetes and reach ESRD have a poor prognosis, having high cardiovascular risk (1). Thus, early identification of patients who have diabetes and are at high nephropathy risk and initiation of nephroprotective treatment is mandatory to prevent the progression and, possibly, the development of DN. This article briefly reviews the effects of antihypertensive agents and the importance of treating multiple risk factors to achieve effective nephroprotection.

Antihypertensive Treatment

Hypertension is an important risk factor for the development of DN and a crucial progression promoter (1). Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) have been suggested to confer additional nephroprotection in diabetes, beyond their effects on BP.

The effects of antihypertensive therapy on the development of nephropathy have been tested in several studies. The Euclid study did not detect any difference in the rate of development of microalbuminuria (MA) in patients who had type 1 diabetes and were treated for 2 yr with lisinopril compared with placebo (2). In patients with type 2 diabetes, tight BP control did not reduce the development of MA in the UK Prospective Diabetes Study (UKPDS) (3); similarly, in the Microalbuminuria Heart Outcomes Prevention Evaluation Study (Micro-HOPE) study, there was no difference in the development of MA between patients who received ramipril and placebo (4). Only the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial described a significant reduction in the rate of development of MA in normotensive patients with type 2 diabetes on strict BP regimen (with no difference between nisoldipine and enalapril) (5), whereas there was no effect in the hypertensive cohort (6).

The impact of antihypertensive therapy in secondary prevention is well established. Indeed, several studies have demonstrated that ACE-I are effective in reducing the progression from MA to overt nephropathy in both type 1 and type 2 diabetes. Although it has been hypothesized that this beneficial effect is largely BP independent, it should be kept in mind that most studies on the effects of ACE-I in MA patients with type 1 diabetes have been performed *versus* placebo, with slight but significant differences in BP between groups (7). In the Micro-HOPE, which involved a large number of patients with type 2 diabetes, MA patients who received ramipril had a reduced progression rate to proteinuria (4). However, there were significant differences in BP between groups; also the development of proteinuria was a secondary end point. In the ABCD trial, aggressive BP control slowed progression to proteinuria in normotensive (5) but not in hypertensive patients with type 2 diabetes and MA (6). The largest trial performed so far in patients with MA, the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study, demonstrated a strong nephroprotective effect of irbesartan in type 2 diabetes (8). In this

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study, 590 hypertensive patients with type 2 diabetes were randomized to receive 300 mg of irbesartan or 150 mg or placebo, along with other antihypertensive agents (with the exclusion of ARB, ACE-I, and calcium channel blockers [CCB]) and followed for 24 mo. Patients who received 300 mg of irbesartan had a significant reduction in the risk to develop proteinuria (70% relative risk reduction *versus* placebo), whereas the achieved BP levels during the study were superimposable in the three groups. Also, the number of patients who regressed to normoalbuminuria was higher in the group that received high-dose irbesartan (34%; 24% in the irbesartan 150 mg and 21% in the placebo) (9). The Microalbuminuria Reduction with Valsartan (MARVAL) Trial compared the effects of valsartan and amlodipine in 322 patients with type 2 diabetes and MA (9). After 24 wk, patients who were treated with ARB had a higher reduction in AER and a higher regression to normoalbuminuria (30 *versus* 15%) despite similar reductions in BP. Finally, it is in patients with overt nephropathy that the use of antihypertensive agents, especially ACE-I and ARB, have more dramatically changed the natural history and improved renal prognosis. The loss in GFR is closely related to BP levels, especially systolic (10). Numerous studies have been performed using both ACE-I and ARB; here, only the more relevant in terms of duration of follow-up and number of patients are summarized. In patients with type 1 diabetes, ACE-I have been shown to reduce the risk for doubling serum creatinine (DSC), reaching ESRD, and death: 409 patients with overt nephropathy were randomized to receive either captopril or placebo for a follow-up of 4 yr (11). Captopril treatment was associated with a 48% reduction in the risk for DSC, which was interpreted to be independent of the small but significant difference in BP between the groups (11). In patients with type 2 diabetes, only small trials have been performed using ACE-I with conflicting results. In contrast, two large randomized, long-term studies showed that ARB are effective in slowing progression of nephropathy in patients with type 2 diabetes and frank proteinuria and mild to moderate renal failure. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study, 1513 patients were randomized to either losartan or placebo (in addition to conventional therapy, excluding ACE-I and ARB) and followed for 3.4 yr (12). Compared with the placebo group, patients who received losartan had a risk reduction of 25% for DSC and of 28% for reaching ESRD (12). In the Irbesartan Diabetic Nephropathy Trial (IDNT), 1715 patients were randomized to receive irbesartan, amlodipine, or placebo (in addition to conventional therapy, excluding ACE-I, ARB, and CCB) and followed for 2.6 yr (13). Irbesartan-treated patients had a risk reduction for DSC of 33% compared with the placebo group and of 37% compared with the amlodipine group (13). In addition, patients who were treated with both losartan and irbesartan had a greater reduction in AER than the other groups. Overall, the results of these studies have demonstrated that the nephroprotective effects of ARB occurred over and above what might be expected from the reduction in BP. These findings have led the American Diabetes Association to recommend the use of ARB for the treatment of patients with type 2 diabetes and proteinuria or MA (14), whereas ACE-I are indicated for patients with type 1 diabetes. These clinical recommendations are obviously based on the available evidence; indeed, large studies on the effects of ACE in patients with type 2 diabetes and proteinuria and of ARB in type 1 diabetes are lacking. It would be of great interest to have direct comparisons between ACE and ARB to examine their effects on progression of DN. So far, the only available study is the recently-completed Diabetics Exposed to Telmisartan and Enalapril (DETAIL) Study, which describes a similar renoprotective effect of enalapril and telmisartan in patients with type 2 diabetes and early nephropathy (mainly microalbuminuria) (15). Finally, the possibility that the association of ARB and ACE-I may confer additional renoprotection in DN has been tested in several small and short-term studies, and further studies are necessary.

Other Aspects of Nephroprotection: Control of Glucose and Lipid Levels

Together with an adequate management of arterial hypertension, it is important to apply some other strategies in preventing progression and even more development of DN. The presence of hyperglycemia is necessary for the development of DN; however, the degree of metabolic control that is able to protect patients from the renal complication has been debated. The Diabetes Control and Complications Trial Research Group in type 1 diabetes (16) and the UKPDS in type 2 diabetes (17) have shown a linear direct relationship between hyperglycemia and both development and progression of renal damage. In the UKPDS, any decrease of HbA_{1c} by 1% was accompanied by a 37% decrease in the incidence rate of micro-macroalbuminuria and retinal complications, and this was true (*1*) also below a 7.0% level of HbA_{1c} and (*2*) irrespective of the pharmacologic treatment. The positive effect of a strict metabolic control lasts even after discontinuing the treatment, as documented by the Epidemiology of Diabetes Interventions and Complications (EDIC) study (18). These and other observations discussed extensively by other authors in this supplement strongly support the importance of pursuing the ideal "renoprotective" glycemic values (HbA_{1c} <7%, preprandial plasma glucose between 90 and 130 mg/dl, and postprandial peak <180 mg/dl [14]). This ambitious target, which is not easy to be pursued despite intensive therapeutic efforts, however, is crucial, taking into account that a prolonged condition of normoglycemia, as that obtained by a successful pancreas transplantation, is even able to revert completely the histologic lesions of DN back to normal (19).

In type 1 diabetes, tight glycemic control is associated with normal lipoprotein levels; conversely, patients with type 2 diabetes are frequently characterized by lipid abnormalities, mainly elevated levels of triglycerides and low HDL levels; moreover, LDL may show important qualitative differences in the pattern that contribute to the increased risk for cardiovascular disease. In humans, dyslipidemia is considered a factor that contributes to the worsening of renal function in patients with preexisting nephropathies (20) as well as a predictive factor for the decline of creatinine clearance in the general population (21). Several cell types could be involved in the

glomerular injury induced both by hypercholesterolemia and hypertriglyceridemia, such as mesangial cells and podocytes; such podocyte damage is accompanied by tubulointerstitial cell activation and injury (22).

Although dyslipidemia may aggravate renal disease, the evidence that correction of lipid abnormalities slows progression to renal failure is still lacking, given that there have been no large randomized, placebo-controlled trials to show the effect of lipid lowering in these patients; nevertheless, the beneficial outcome of treating dyslipidemia in the diabetic population in general supports aggressive therapy when nephropathy develops. 3-Hydroxy-3-methylglutaryl-CoA reductase inhibition seems to confer renoprotection (23); it is not yet fully understood whether this effect is only due to the reduced LDL levels, or the effects on prosclerotic cytokines and macrophage accumulation, combined with an improved endothelial function, might play an additional role. Fibrates might be an alternative, especially in patients with low HDL cholesterol and high triglycerides. Combination of the two compounds should be avoided in renal failure.

Importance of a Multifactorial Approach

The most relevant piece of evidence on the beneficial effect of a multifactorial approach in preventing the development of proteinuria in diabetes is the Steno 2 Study (24), where 160 MA patients with type 2 diabetes were randomly assigned to receive standard diabetes care (from the general practitioners) or an intensive therapeutic program at the Steno Diabetes Center, consisting of advice about an appropriate diet and exercise regimen; smoking-cessation programs; intensive treatment of hyperglycemia, hyperlipidemia, and hypertension; use of an ACE-I (irrespective of BP); use of antioxidants; and use of aspirin in patients with any evidence of peripheral vascular disease. The primary end point was to reduce the progression to overt DN; secondary end points were to limit incidence and progression of retinopathy and neuropathy. On the basis of the natural history of microangiopathic complications in type 2 diabetes, every year, 4 to 8% of these patients are expected to progress toward overt nephropathy or retinopathy; after 4 yr of follow-up, patients who received intensive and multiple treatment had approximately 50% reduction of progression of microvascular complications (mean odds ratio [OR], 0.27 for nephropathy, 0.45 for retinopathy, and 0.32 for neuropathy).

In 2003, the authors published the results after 7.8 yr of follow-up, concerning data of 63 patients who were under the conventional regimen and 67 who were under intensive therapy (25). This study, whose primary end point was a composite of cardiovascular events, showed an impressive reduction in these events (mean OR, 0.47, equivalent to a number needed to treat for 7.8 yr of 5), as well as significant reductions in DN (mean OR, 0.39) and retinopathy (OR, 0.42), however, not dissimilar from those observed after 4 yr.

The results of the Steno 2 are likely to be due to a combination of the interventions used and the different settings in which the groups were followed up, and it is impossible to dissect which component of the "package" of interventions provided the greatest benefit. The study has the great merit to have demonstrated that pharmacologic therapy targeting glucose, BP, and lipid-defined goals, along with the use of aspirin, exercise, and a proper diet, effectively reduces the risk of the chronic complications of diabetes. Thus, a good management of diabetes, based on a multifactorial approach, represents the best preventive medicine that we can practice. This trial also revealed the difficulties to reach the targets and the limitations of current therapies and strategies: Blood glucose targets were achieved in only 15% and systolic BP in <50% of patients who received intensive treatment, and smoking cessation advice was ineffective in both groups. It is likely that even greater benefits may be possible if newer treatments could allow more often the achievement of the targets recommended by current guidelines.

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