Does Antihypertensive Treatment Prevent Progression of Microalbuminuria to Overt Proteinuria in Insulin-Dependent Diabetic Patients?

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ABSTRACT
Prospective studies in insulin-dependent diabetic patients have shown that microalbuminuria is a strong predictor of clinical nephropathy. Because this syndrome is associated with a dramatic excess in mortality, different types of intervention have been proposed for insulin-dependent diabetic patients with microalbuminuria to prevent or postpone clinical nephropathy. The effects of antihypertensive treatment are being extensively investigated. Beta-blockers, calcium antagonists, and angiotensin-converting enzyme inhibitors have proved effective in reducing albumin excretion and postponing overt proteinuria in hypertensive and normotensive insulin-dependent diabetic patients with microalbuminuria. However, many problems remain to be solved. A decrease in albumin excretion may not be an adequate endpoint for intervention trials, because it has been shown that patients with normal albumin excretion can develop diabetic nephropathy lesions, whereas patients with microalbuminuria alone may have little or no pathology. The patients included in these trials all had incipient diabetic nephropathy but exhibited different functional, and probably morphological, forms of the disease. For insulin-dependent diabetic patients with microalbuminuria, the real aim of antihypertensive treatment is not to reduce urinary albumin excretion or to prevent its progression but to preserve renal function and to reduce the incidence of premature cardiovascular deaths. To achieve this, we have to improve our knowledge of the natural history of the early pathology of diabetic nephropathy and of the mechanisms of action of antihypertensive treatment. New large-scale intervention trials will have to be designed in which the patients will have to be carefully characterized on the basis of functional and morphological data. Long-term, multicenter intervention trials should assess the effects of various antihypertensive regimens that may alter not only the evolution of diabetic glomerulopathy, but also the development of atherosclerosis.

Key Words: GFR, pathology, diabetic nephropathy, angiotensin-converting enzyme inhibition, calcium antagonism

Thirty to forty percent of patients with insulin-dependent diabetes mellitus (IDDM) develop clinical nephropathy. This syndrome is defined by persistent albuminuria over 300 mg/24 h (overt proteinuria), raised blood pressure values, and a linear decline in the GFR (1). IDDM patients with clinical nephropathy suffer a dramatic excess in mortality mainly due to end-stage renal failure and coronary events (2). Arterial hypertension aggravates the evolution of diabetic kidney disease, but effective antihypertensive treatment reduces albuminuria and the rate of decline in GFR and consequently postpones end-stage renal failure (3, 4). During the last few years, the prognosis of clinical diabetic nephropathy has improved, probably as a consequence of early aggressive antihypertensive treatment (5) and better health care delivery to IDDM patients. Nevertheless, diabetic nephropathy is currently the leading cause of end-stage renal disease in Europe and the United States. IDDM patients at risk of developing clinical nephropathy may be identified by the detection of persistent microalbuminuria (30 to 300 mg/24 h) i.e., an albumin excretion rate (AER) above normal values but below those giving positive results on dip-stick testing (6). A small increase in blood pressure (BP) values is an early and common finding in diabetic patients with microalbuminuria (7). In a proportion of such patients with the so-called incipient nephropathy, abnormal renal hemodynamics resulting in glomerular hyperfiltration can be detected and may be determinants in the development of clinical nephropathy (8). Prospective studies have shown that microalbuminuria is a strong predictor of clinical ne-
phropathy in IDDM (9–11). The prevalence of microalbuminuria was about 20% in IDDM patients attending diabetic clinics (12,13).

During the last decade, several types of intervention have been proposed for diabetic patients with incipient nephropathy in an effort to prevent the onset of clinical nephropathy.

Strict glycemic control achieved with continuous s.c. insulin infusion (CSII) can reverse glomerular hyperfiltration due to poor metabolic control, but at least 2 yr of treatment must be given to prevent clinical nephropathy from developing (14). The long-term analysis lasting 5 or 8 yr of the Steno studies suggests that patients at risk for clinical nephropathy should be offered near-normal glycemic control in order to alter AER evolution, because among the 19 patients who were at severe risk for clinical nephropathy (AER, 100 to 300 mg/24 h), two out of nine in the insulin infusion group versus 10 out of 10 on conventional treatment developed clinical nephropathy. However, insulin infusion in these studies was associated in three patients with lethal ketoacidosis—7 out of 34 patients on CSII at entry were on multiple insulin injections at reexamination, and 7 patients on CSII were on antihypertensive treatment at reexamination (15). The results of the ongoing DCCT trial may demonstrate that long-term improvement in glycemic control in a large cohort of patients is feasible and safe and prevents or postpones clinical nephropathy in microalbuminuric patients (16). At the present time, however, such evidence is still lacking. The restriction of dietary protein can reduce AER and glomerular hyperfiltration in small groups of motivated patients (17), but no study has demonstrated that diabetic patients will comply with such a diet in the long term. Aldose reductase inhibition has proved effective in diabetic animal models, and in the short term, has reduced AER in IDDM patients with microalbuminuria (18). However, to date, the safety and long-term efficacy of such an intervention have not been documented in IDDM patients with microalbuminuria.

In the first part of this article, I review the most important studies in which antihypertensive treatment was used to alter the natural course of incipient diabetic nephropathy in humans. The results of these studies indicate that for IDDM patients with microalbuminuria, early antihypertensive treatment appears to be the most effective and the easiest way of intervention to prevent the development of overt proteinuria. However, many problems are still to be solved or remain controversial; they will be discussed in the second part of the article in light of the experimental studies that have improved our knowledge of the pathophysiology of diabetic glomerulopathy and the mechanisms of the effects of various antihypertensive regimens.

ANTIHYPERTENSIVE TREATMENT IN IDDM PATIENTS WITH MICROALBUMINURIA—PART I.

RESULTS

To our knowledge, the first study dealing with the effect of antihypertensive treatment on the progression of incipient diabetic nephropathy was reported by Christensen and Mogensen in 1985 (19). Six male IDDM patients with microalbuminuria and slightly elevated BP were monitored for a mean duration of 5.4 yr with repeated measurements of AER before and during a treatment with the cardioselective beta-blocker, metoprolol (200 mg daily). The mean yearly increase in AER was 18 ± 17% before treatment, whereas AER decreased by 17 ± 15% yearly during treatment. Concomitantly, mean arterial pressure was reduced from 107 ± 7.6 to 97 ± 3.4 mm Hg. No change was observed in RPF or GFR. These results were confirmed by Friedman et al. in similar patients in a short-term study during which metoprolol administration, withdrawal, and rechallenge were associated with concomitant variations of AER and BP in four patients out of five (20). Hommel et al. reported that AER in IDDM patients with microalbuminuria was acutely reduced over a short period of time when patients were given clonidine (21). The next study was conducted by Michel Marre in our group (22,23). Twenty "normotensive" diabetic patients (BP, <160/95 mm Hg) who had persistent microalbuminuria were randomly allocated for 1 yr to 20 mg once daily of either the ACE inhibitor enalapril or a placebo. Before treatment, both groups displayed similar clinical characteristics; thus, the median AER was 124 mg/24 h in the enalapril group and 81 mg/24 h in the placebo group, and the corresponding mean arterial pressures were 100 (±8 SD) and 99 (±6 SD) mm Hg. During the last 3 months of the trial, the AER was reduced in all patients on enalapril and five of them had normal AER of <30 mg/24 h. Three patients in the placebo group developed clinical nephropathy with AER of >300 mg/24 h. Mean arterial pressure was reduced by enalapril throughout the study (P < 0.005) but increased linearly with placebo (P < 0.05). An increase in the AER was positively related to the increase in mean arterial pressure. There was no change in the median GFR in the enalapril group, but a decrease from a value of 129 to 109 mL/min/1.73 m² was observed in the placebo group. The finding that angiotensin-converting enzyme inhibition can reduce microalbuminuria and prevent overt proteinuria, even in the absence of hypertension, was promising but should be interpreted with caution, because the treatment with enalapril lasted for only 1 yr and longer studies were needed to confirm the beneficial effects of ACE inhibition not only on AER but also on the evolution of GFR. When the study was conducted the potential...
long-term side effects of ACE inhibition were not yet known. It was not clear whether the reduction in AER was due to the decrease in systemic BP independently of the antihypertensive regimen used or to specific changes in intraglomerular pressure related to ACE inhibition. Last, the reduction in microalbuminuria could be only an index of the mechanical consequences of the reduction in systemic BP, glomerular pressure, or both. We did not have any evidence of a concomitant reduction in morphological glomerular lesions.

The main objective of the studies that followed was to compare the effects on BP and AER of ACE inhibitors and calcium antagonists. Thus, in the trial by Mimram et al. (24), the effects of a 6-wk treatment with placebo, 20 mg of nifedipine twice daily, or 25 mg of captopril twice daily were assessed in three groups of seven normotensive IDDM patients with microalbuminuria. In response to captopril and nifedipine, BP decreased slightly and to a similar extent; however, these drugs resulted in opposite effects on AER because it rose by 40% during nifedipine treatment and decreased by 40% with captopril. No change in AER was observed in the placebo group. The observation of opposite effects in AER in the presence of a similar decrease in arterial pressure suggests that the effects of these drugs result from differences in their intrarenal action. Unfortunately, renal hemodynamics and GFR were not evaluated during this study (24).

To compare the efficacy of ACE inhibition and calcium antagonism in diabetic patients with microalbuminuria was also the goal of the trial reported by the Melbourne Diabetic Nephropathy Study Group (25). Forty-three diabetic patients completed this randomized study: 19 had IDDM, 24 had non-insulin-dependent diabetes mellitus, 30 were normotensive (BP, <160/95 mm Hg), and 13 were hypertensive. For 12 months, 20 patients were given 2 to 8 mg daily of the ACE inhibitor perindopril and 23 were given 20 to 80 mg daily of nifedipine. They were monitored for 1 or 3 months after treatment was stopped depending on whether they were hypertensive or normotensive. Both perindopril and nifedipine significantly reduced mean BP. During treatment, there was no significant difference between those treated with perindopril and those treated with nifedipine with regard to albuminuria or mean BP levels. There were significant correlations between mean BP and albuminuria and also between the reduction in mean BP and the decrease in albuminuria during both treatments. In the hypertensive patients, both drugs significantly reduced mean BP and albuminuria. In the normotensive patients, there was no significant reduction in albuminuria with either regimen. Stopping treatment with both drugs was associated with a sustained increase in albuminuria and mean BP. In conclusion, perindopril and nifedipine had similar effects on AER, both preventing increases in albuminuria in normotensive patients and decreasing albuminuria in hypertensive patients (25). The evolution of AER and BP values after stopping antihypertensive treatment is worth consideration. We had the opportunity to make the following observations. In 12 diabetic patients with microalbuminuria or overt proteinuria, long-term ACE inhibition with 20 mg of enalapril daily for a mean duration of 36 months significantly reduced BP and AER. A 2-month placebo period was associated in all of these patients with a fast rise in BP and a dramatic increase in albuminuria. When ACE inhibition was reintroduced, AER and BP returned to preplacebo values (26). These data indicate the need for permanent ACE inhibition in patients with microalbuminuria and suggest that the pathological process related to albuminuria may have remained unchanged despite long-term ACE inhibition.

Finally, the effectiveness of ACE inhibition in preventing, in the long term, the development of overt proteinuria was assessed by the study recently reported by Mathiesen et al. (27). This controlled trial of 4 yr duration included 44 normotensive patients (mean BP, 127/78 ± 12/10 mm Hg) with IDDM and persistent microalbuminuria. Twenty-one were randomly allocated to 100 mg of captopril daily with a thiazide added after 30 months, and the remaining 23 patients were left untreated. Clinical and laboratory variables were comparable at baseline in both groups. AER was gradually reduced from a geometric mean of 82 to 57 mg/24 h in the captopril group, whereas it rose from 105 to 166 mg/24 h in the untreated control group (P < 0.05). Seven of the untreated patients progressed to overt proteinuria versus none in the captopril group. Systemic BP, GFR, hemoglobin A1c, and urinary excretion of sodium and urea remained practically unchanged in the two groups. No side effects were observed in the captopril group. These results confirm and extend those reported by Marre et al. (22,23) and suggest that in normotensive IDDM patients with persistent microalbuminuria ACE inhibition postpones and may prevent the development of clinical nephropathy (27). The absence of a significant modification in BP values in the captopril-thiazide group is surprising and is discordant with the results observed in our group (23). It suggests that intrarenal inhibition of the renin-angiotensin system has a specific effect on glomerular permeability to albumin.

In summary, the data in the literature clearly show that various antihypertensive regimens, including beta-blockers, ACE inhibitors, and calcium antagonists, may reduce AER or prevent its increase in IDDM patients with microalbuminuria, whether they are hypertensive or normotensive. So, from a clinical point of view to the question: does antihypertensive
treatment prevent overt proteinuria in IDDM patients with microalbuminuria? The answer is yes. However, the real aim of such treatment is not to reduce AER or to prevent its progression, but in the long term, to prevent the decline of GFR, end-stage renal failure, and cardiovascular death. To achieve this, many problems are still to be solved.

PART II. DISCUSSION
In Intervention Trials, a Decrease in AER May Not Be an Adequate Scientific Endpoint

Despite the large number of studies devoted to early diabetic nephropathy in IDDM patients during the last decade, very little is known about the natural history of the early pathology of diabetic nephropathy. This is because of the lack of information regarding the interrelationship of epidemiological, genetic, clinical, and renal functional variables with the early nephropathological consequences of diabetes. For example, it has been shown that some patients with normal AER developed diabetic nephropathy lesions including fractional mesangial expansion, whereas others without albuminuria alone had little or no pathology (28). Microalbuminuria at levels found positive for the development of overt proteinuria were frequently accompanied by increased BP, decreased GFR, or both, as well by more advanced renal lesions. In these patients, microalbuminuria was in fact a marker of early clinical nephropathy. At this stage, efforts to really prevent the evolution of the critical morphological lesions and the deterioration of renal function may be unlikely to succeed. Because structural diabetic renal lesions can develop in the absence of microalbuminuria and because microalbuminuria may be associated with no change, minimal change, or significant morphological kidney lesions, a decrease in AER or the prevention of overt proteinuria may not be in itself an adequate endpoint in intervention trials. However, it should be recalled that in the Steno studies (CSII versus conventional insulin treatment), a significant yearly reduction in GFR was found only in patients who developed clinical nephropathy, whereas GFR remained normal or supranormal in patients who did not (15).

The Selection of the Patients Included in Intervention Trials May Be Inadequate

It must be noticed that in the study by Marre (22,23) and in the Melbourne Diabetic Nephropathy Study (25), the included patients were IDDM and NIDDM patients. Because the prevalence of microalbuminuria is about 20% in IDDM patients attending diabetic clinics, it is remarkable that all of these studies were dealing with relatively small groups of patients; a selection bias may be present, restricting the conclusions to the most motivated and compliant patients.

To qualify for participation in the trials reviewed here, individuals with incipient nephropathy had to have microalbuminuria either in the lower range of 30 mg/24 h in two determinations out of three or in the upper range of 200 to 300 mg/24 h. With regard to BP values, they could be either hypertensives according to the World Health Organization criterion of >160/95 mm Hg, normotensives according to the Working Group on Hypertension in Diabetes BP of <140/90 mm Hg (29), or not hypertensives with BP values between these two ranges. BP values were recorded by the same observer or different nurses or doctors with a mercury sphygmomanometer, a random zero manometer, or an automatic device. A proportion of patients had an increased GFR, which was normal or slightly decreased in others. These patients all had the clinical condition of incipient diabetic nephropathy but exhibited different functional, and probably morphological, forms of kidney disease. These considerations may explain some of the discordant results and suggest that, in the long run, antihypertensive treatment may have different effects in patients in reducing AER and in preventing decline in renal function. Therefore, in the future, it is mandatory to improve our knowledge of the natural history of early diabetic nephropathy, and the design of intervention trials should take into account the need for more accurate characterization of the patients to be included. Histological data will be very useful in assessing the effectiveness of different antihypertensive regimens.

The Mechanisms of Action of Antihypertensive Agents in Early Diabetic Nephropathy Are Still Poorly Known

The mechanism that accounts for the relationship between albumin excretion and blood pressure remains unclear. The most likely explanation is that BP is one of the determinants of intraglomerular pressure and that BP is one of the factors that influences the magnitude of albumin leakage through a porous glomerular membrane. If this explanation is correct, decreasing BP, while temporarily lowering the rate of albuminuria, might have no long-term effect in slowing down the progression of kidney disease. The fast rise in albuminuria observed after antihypertensive treatment withdrawal is in keeping with this hypothesis. On the other hand, it is also possible that in addition to affecting the magnitude of the glomerular albumin leakage, high BP might contribute to the progression of the structural kidney lesions. The results from animal studies support the possibility that high BP contributes to glomerular ultrastructural changes and that they can be mini-
mized or prevented by various antihypertensive agents (see Sharon Anderson's paper).

The Antiproteinuric Effect of ACE Inhibition

From the data in the literature concerning humans and animal models, it may be assumed, despite some conflicting results, that ACE inhibitors reduce proteinuria more effectively than do other antihypertensive agents. The mechanisms of the antiproteinuric effect of ACE inhibition are still poorly understood. For instance, it is not yet known whether the decrease in BP that accompanies ACE inhibition, even if this decrease is modest, in itself explains the decrease in albuminuria or whether the most likely explanation is the intrarenal inhibition of the renin-angiotensin system through the reduction of intraglomerular pressure, an enhanced intrinsic selectivity of the glomerular barrier wall, or both. Morelli et al. (30), who studied the sieving profile of neutral dextran during ACE inhibition in normotensive IDDM patients with AER over 50 μg/min, found that enalapril for 90 days significantly reduced fractional dextran clearance and systemic BP. Withdrawal of the drug for 30 days was associated with a return to pretreatment levels for BP and the dextran sieving profile. They concluded that ACE inhibition diminishes glomerular permeability to proteins by enhancing barrier size selectivity, because neither enalapril nor its withdrawal significantly influenced renal hemodynamics; they proposed that the primary action of enalapril is to modulate the intrinsic membrane properties of the glomerular barrier (30). Whatever the real mechanisms of the antiproteinuric effect of ACE inhibition, it may be speculated that the reduction in the transcapillary protein traffic across the glomerular capillary wall would attenuate protein accumulation in the mesangium. Because this accumulation may stimulate mesangial cell proliferation, mesangial matrix production, and possibly glomerular sclerosis, reduced protein circulation through the mesangium would, in the long run, slow down the progression of renal disease.

CONCLUSION

During the last decade, our knowledge of diabetic kidney disease has greatly improved. The role of arterial hypertension in the evolution of diabetic glomerulopathy has been established, as well as the beneficial effect of early antihypertensive treatment in reducing AER and postponing or preventing overt proteinuria in IDDM patients with microalbuminuria. Nevertheless, many aspects of the relation between arterial hypertension and diabetic kidney disease are still poorly known, and too many patients still suffer from end-stage renal failure and premature cardio-vascular death. Future clinical research in the early stages of diabetic nephropathy must develop in different directions. The natural history of the early pathology of diabetic nephropathy is to be established in relation to its putative determinant and protective factors. To achieve such a goal will require a long-term, multidisciplinary complex study including a large number of carefully selected and accurately classified IDDM patients undergoing renal biopsies. The genetic material obtained from these patients may provide an answer to the crucial question of why the majority of IDDM patients never present with albuminuria, whereas some individuals rapidly progress to severe kidney disease, despite moderate hyperglycemia and apparently effective antihypertensive treatment. Systemic BP may be one major protective or determinant factor for the progression in diabetic nephropathy. The commonly used classification of microalbuminuric patients as hypertensive or normotensive is obviously inadequate. The detection of more subtle differences in BP may require improved technologies; 24-h ambulatory monitoring and home self-monitoring may be useful guidelines for the initiation and adaptation of antihypertensive treatment. At the present time, to reduce systemic BP values to less than 140/90 mm Hg in the clinic is the objective for patients in the early stages of diabetic nephropathy. These target values may be obsolete if a more significant decrease in BP is proved feasible and safe and is combined with prevention of a decline in GFR and of coronary heart disease. In this connection, it should be recalled that IDDM patients apparently free of complications for more than 40 yr have lower BP than age- and sex-matched nondiabetic controls. In the future, new types of intervention trials have to be designed. The patients to be included will have to be carefully characterized on the basis of functional and morphological data. Large-scale, long-term multicenter intervention trials will be necessary to compare the effects of various antihypertensive regimens that may alter not only the evolution of diabetic glomerulopathy but also the development of atherosclerosis.

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