Renoprotective role of ACE inhibitors in diabetic nephropathy

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Patients with diabetes mellitus and overt proteinuria have a poor prognosis.¹ Recent studies show that appreciable proteinuria is associated with a much more rapid progression of disease than is moderate albuminuria.² Progression is also closely associated with raised blood pressure, but appreciable albuminuria in itself seems to be an important prognostic indicator.

Before clinical proteinuria occurs (macroalbuminuria) patients always go through a stage of microalbuminuria, often lasting 10 years. Diabetic renal disease develops in stages, especially in patients with insulin dependent diabetes.³⁻⁵ Classification according to the degree of albuminuria is important because patients with perfectly normal albumin excretion rates usually have a good long term prognosis, although some (about 4% per year) of them will progress from normoalbuminuria to microalbuminuria.⁶ On the other hand, patients with persistent microalbuminuria have (without intervention) a much poorer prognosis, with a much higher risk of progression to overt renal disease over the following decade.³ According to new morphometric studies, this is not surprising because microalbuminuria indicates that patients are in a more advanced stage of glomerular disease.⁷

In this paper I will review data on intervention with ACE inhibitors throughout the course of diabetes. Editorials in three major journals recently discussed this important issue.⁸⁻¹⁰ Table 1 shows an outline of the stages of diabetic renal involvement and disease in patients with insulin dependent diabetes from the time of diagnosis of

diabetes. Poor glycaemic control is an important factor determining transition to microalbuminuria and probably progression of the microalbuminuric state,^{6 11 12} but metabolic control is difficult in these patients.

Occurrence of raised blood pressure in renal diabetic disease

INSULIN DEPENDENT DIABETES MELLITUS

The prevalence of hypertension in patients with insulin dependent diabetes defined according to the World Health Organisation's classification, and including patients receiving treatment, is similar in patients with normoalbuminuria and the general population.¹³ The prevalence of hypertension increases sharply in patients with microalbuminuria, and most patients with overt proteinuria have classic hypertension. Soon after the occurrence of microalbuminuria, blood pressure may increase by about 4 mm Hg per year.⁶ Therefore the main group of patients with insulin dependent diabetes that are given antihypertensive treatment are those with microalbuminuria or overt renal disease. On the other hand, some patients with insulin dependent diabetes may have raised blood pressure before microalbuminuria—that is, coincidental essential hypertension.¹³ Also, it is important to note that some patients with normoalbuminuria will develop microalbuminuria. This is part of the natural course of the disease because during the first few years of diabetes most patients after metabolic stabilisation will have normoalbuminuria. Renal damage clearly increases the longer the duration of diabetes.

Table 1 Stages of renal disease* in patients with insulin dependent diabetes

Stage	Designation	Main characteristics	Main structural changes	Glomerular filtration rate (ml/min)	Urinary albumin excretion	Blood pressure	Comments
I (at diagnosis)	Hyperfunction/hypertrophy†	Glomerular hyperfiltration	Glomerular hypertrophy	≈ 150	May be increased	Normal	Glomerular volume/pressure increase (reversible)
II	Normoalbuminuria	Normal urinary albumin excretion	Increasing basal membrane thickness	Hyperfiltration‡	Normal (high during stress)	Normal	Changes as indicated above but quite variable
Transition from II → III	Transition phase	High normal urinary albumin excretion	Not known	Hyperfiltration	Increasing	Increasing	Somewhat poor metabolic control
III	Incipient diabetic nephropathy, microalbuminuria	Raised urinary albumin excretion	Urinary albumin excretion correlated to structural damage	Still high	20 → 200 µg/min	Raised compared with stage II	Advancing glomerular lesions; permeability defect not located
IV	Overt diabetic nephropathy	Clinical proteinuria or urinary albumin excretion > 200 µg/min	Advanced structural damage	"Normal" to advanced reduction	> 200 (→ ≈ 10 000 µg/min)	Often frank hypertension increase by ≈ 5% yearly	High rate of glomerular closure; severe mesangial expansion
V	End stage renal disease	Uraemia	General glomerular closure	Very low	Decreasing albuminuria	Often high, related to volume expansion	Death/uraemia (postponed by ACE inhibition)

*Applied when blood pressure remains untreated. Reducing blood pressure often reduces albuminuria (proteinuria → microalbuminuria → normoalbuminuria).

†Changes present probably in all states when control imperfect.

‡Marker of future nephropathy.

NON-INSULIN DEPENDENT DIABETES MELLITUS
The situation in patients with typical non-insulin dependent (type 2) diabetes is somewhat different.¹⁴ Many of these patients have hypertension when diabetes is diagnosed, and they may have renal complications when they are first seen. According to a recent survey in general practice in Denmark, more than 30% of patients with newly diagnosed diabetes had microalbuminuria and about 6% clinical proteinuria, with a male preponderance.¹⁴ There is a weak correlation between the degree of albuminuria and blood pressure. Also, many patients are already receiving antihypertensive treatment. Albuminuria also correlated with degree of glycaemia and with triglyceride concentrations. With more advanced renal disease blood pressure tended to increase further, and an even larger proportion of patients require antihypertensive treatment when overt renal disease is present.¹⁵

Transition from normoalbuminuria to microalbuminuria

INSULIN DEPENDENT DIABETES MELLITUS

New studies measuring ambulatory blood pressure have clearly indicated that transition from normoalbuminuria to microalbuminuria is associated with a concomitant increase in ambulatory blood pressure over 24 hours. The onset of microalbuminuria is always associated with a rise in blood pressure, but the converse is not necessarily true.⁶ In patients developing microalbuminuria the increase in blood pressure was fourfold compared with that in those patients who did not do as well as healthy controls. Therefore, early in the course of renal complications, raised blood pressure is important, although it is difficult to outline clearly the prime abnormality as patients developing microalbuminuria already have albumin excretion rates in the upper part of the normal range, around 10 $\mu\text{g}/\text{min}$. These observations suggest a radical new preventive approach. Maybe patients with normoalbuminuria at risk of renal progression should in the future be treated with antihypertensive agents even if they do not have high blood pressure. An important recent prospective study also shows that transition from normo-

albuminuria (defined as $< 30 \mu\text{g}/\text{min}$: a rather high value) to microalbuminuria ($\geq 30 \mu\text{g}/\text{min}$) is associated with higher initial albumin excretion as well as some hypertension.¹² In patients with microalbuminuria even slight increase in blood pressure promotes progression.³

NON-INSULIN DEPENDENT DIABETES MELLITUS

Usually there is a gradual increase in albuminuria with time in patients with non-insulin dependent diabetes. In the normoalbuminuric stage, however, many patients remain stable despite a long duration of diabetes.¹⁶ Albuminuria increases by about 20% per year, and this is related to the attained blood pressure (A Schmitz, personal communication). This again suggests the deleterious effect of even a slight increase in blood pressure in type 2 diabetes. Glycaemic control is also likely to be affected, but so far there are no published long term studies on optimised diabetes control in patients with type 2 diabetes, although important work is in progress.¹⁷ Many patients with type 2 diabetes are elderly and have confounding risk factors, so it is hazardous to extrapolate the encouraging data on glycaemic control in patients with type 1 diabetes to this population.¹¹

Clinical trials in patients with normoalbuminuria

INSULIN DEPENDENT DIABETES MELLITUS

ACE inhibition in patients with albuminuria is associated with a significant reduction in filtration fraction and fractional albumin clearance (fig 1).¹⁸ Importantly, in this study there was no significant change in clinic based blood pressure, although ambulatory blood pressure over 24 hours was not measured. The reduction in filtration fraction could, in theory, be associated with a decrease in hydraulic glomerular pressure, which in turn could explain the reduction in albuminuria. Although it is too early to recommend antihypertensive treatment in such patients, this study underlines interest in clinical trials in this area. Patients at risk of developing microalbuminuria—namely, patients with poor metabolic control (glycated haemoglobin ($\text{HbA}_{1\text{C}}$) $> 9\text{--}10\%$), some persistent borderline increase in albumin excretion already ($> 10\text{--}12 \mu\text{g}/\text{min}$), and possibly severe hyperfiltration (glomerular filtration rate $> 150 \text{ ml}/\text{min}$)—should be enrolled in clinical trials to see whether the development of microalbuminuria can be prevented.

NON-INSULIN DEPENDENT DIABETES MELLITUS

Recent studies show that ACE inhibitors reduce blood pressure effectively in patients with non-insulin dependent diabetes, but to reduce albuminuria within normal excretion seems to be difficult. No adverse effect on concentrations of glucose, lipids, or uric acid was seen.^{19 20} Interestingly, low dose diuretic treatment is also effective, which may be because these patients usually retain sodium

Figure 1 Filtration fraction and fractional albumin clearance after three months of placebo or enalapril 30 mg per day in nine patients with insulin dependent diabetes and normoalbuminuria.¹⁸

Table 2 Trials resulting in slightly reduced blood pressure in young non-hypertensive patients with insulin dependent diabetes and microalbuminuria or early nephropathy

Reference (year)	Nature of trial	Intervention	No of patients; duration of treatment	Microalbuminuria	Comments
Christensen and Mogensen ²¹ (1985)	Self controlled, open	β_1 blocker + diuretics	6; 5 years	Reduced	Gradual reversal of albuminuria by antihypertensive treatment
Marre <i>et al</i> ²² (1988)	Double blind, randomised with parallel controls	ACE inhibition	20; 1 year	Reduced by ACE inhibition	Untreated patients showed rapid increase in urinary albumin excretion (also see figure 2)
Brichard <i>et al</i> ²³ (1989)	Open	ACE inhibition	7; 1 year	Reduced by ACE inhibition	
Rudberg <i>et al</i> ²⁴ (1990)	Open	ACE inhibition	12; 6 months	Reduced by ACE inhibition	Young patients
Cook <i>et al</i> ²⁵ (1990)	Cross over, double blind	ACE inhibition	12; 3 months	Reduced by ACE inhibition	Children
Melbourne Diabetic Nephropathy Study Group ²⁶ (1991)	Open, randomised with parallel controls	ACE inhibition v calcium blocker	43; 1 year	Reduced by ACE inhibition and by calcium blocker	Effect mostly seen with raised blood pressure
Mathiesen <i>et al</i> ²⁷ (1991)	Open, randomised with parallel controls	ACE inhibition	44; 4 years	Reduced by ACE inhibition	First study to indicate preservation of glomerular filtration rate; proteinuria prevented
Marre <i>et al</i> ²⁸ (1991)	Double blind, randomised with parallel controls	ACE inhibition	16; 6 weeks	Reduced	Effect surprisingly not dose dependent
Mau Pedersen <i>et al</i> ²⁹ (1991)	Open, cross over	β_1 Blocker + thiazide + ACE inhibition	8; 3 months	Albuminuria reduced	Triple treatment may be useful (early nephropathy)
Mau Pedersen <i>et al</i> ³⁰ (1992)	Cross over, double blind	β_1 Blocker + thiazide + ACE inhibition	10; 4 months	Albuminuria reduced	Triple treatment may be useful (early nephropathy)
Hallab <i>et al</i> ³¹ (1993)	Randomised with parallel controls	ACE inhibition	21; 1 year	Reduced by ACE inhibition	ACE inhibition more efficient than thiazide
Viberti <i>et al</i> ³² (1994)	Multicentre, double blind, randomised with parallel controls	ACE inhibition	92; 2 years	Reduced by ACE inhibition	First large scale double blind study; increase in albuminuria and proteinuria significantly prevented

(S Nielsen, personal communication). It is not yet known whether blood pressure reduction in these patients will result in long term preservation of renal function.

Clinical trials in patients with microalbuminuria

INSULIN DEPENDENT DIABETES MELLITUS
Over the past decade many clinical trials have been conducted in patients with microalbuminuria, especially patients with insulin dependent diabetes.²¹⁻³² Firstly, a β_1 blocker plus diuretics were tested, but latterly ACE inhibitors have been studied in particular (table 2). Clearly, a reduction in or stabilisation of microalbuminuria is consistently observed, and progression to overt proteinuria is prevented by ACE inhibition in some studies.^{22 27 32} This observation is important because in the natural course of diabetes in the

transition of microalbuminuria to macroalbuminuria there is always a fall in glomerular filtration rate.³³ On the other hand, patients who remain microalbuminuric usually have well preserved renal function. These observations suggest that antihypertensive intervention, particularly ACE inhibition, should be started early in the phase of microalbuminuria. Blood pressure was not raised according to the WHO criteria, rather it was close to normal mean values. This suggests that intervention should be started irrespective of blood pressure. However, patients with a moderate increase in blood pressure usually show a more rapid progression in albuminuria and a greater risk of progression to overt renal disease.³ Therefore some increase in blood pressure strengthens the indication for antihypertensive treatment. In clinics patients should be frequently monitored for microalbuminuria, and in the case of increase over several months or even a year antihypertensive treatment should be started. At the same time metabolic control and general diabetes care should be optimised. One long term study clearly suggests that a drop in glomerular filtration rate is prevented by ACE inhibition combined with diuretics.²⁷ This study has now reached eight years with consistent results (E R Mathiesen, personal communication). Only a few side effects were observed in all the trials in table 2. The risk of such intervention is limited and the potential benefit enormous. Recent studies clearly show that from a cost-benefit point of view early antihypertensive treatment in the microalbuminuric state is advisable.³⁴ It is not yet known if early antihypertensive treatment will ameliorate the course of the other complications seen at a much higher prevalence in patients with microalbuminuria, especially heart disease (left ventricular hypertrophy) and advanced diabetic retinopathy. New studies suggest, however,

Figure 2 Median logarithm of albumin excretion in 10 patients with insulin dependent diabetes treated with placebo and 10 treated with enalapril. Shading shows range of values. Blood pressure decreased significantly with enalapril and increased with placebo.²²

Figure 3 Albuminuria and reciprocal serum creatinine concentrations during five years of follow up of patients with non-insulin dependent diabetes treated with enalapril or placebo. Less proteinuria occurred in the enalapril group compared with placebo group after the second year, and the mean rate of decline in reciprocal creatinine concentration differed between the two groups.³⁶

that antihypertensive treatment reduces left ventricular hypertrophy.³⁵

NON-INSULIN DEPENDENT DIABETES MELLITUS
Accumulating evidence suggests that ACE inhibition might be indicated in young patients with type 2 diabetes. Chan *et al* showed that ACE inhibitors effectively reduced microalbuminuria, an effect which was superior to that of the calcium blocker nifedipine, but this was a fairly short study.²⁰ The most impressive study was conducted by Ravid *et al*, comparing enalapril with conventional antihypertensive treatment, to control for changes in blood pressure (fig 3).³⁶ The group given ACE inhibitors showed an initial reduction in albuminuria followed by stabilisation for five years.³⁶ A steady increase was observed in the control group. More importantly, an index of glomerular filtration rate—namely, reciprocal serum creatinine concentration—was stabilised by enalapril, whereas in the control group the reciprocal steadily declined. (Eight year follow up provides similar results (M Ravid, personal communication).) The recent study by

Lacourcière *et al*, shows that microalbuminuria can be reduced by an ACE inhibitor in contrast to conventional treatment,¹⁹ but they did not find an effect on glomerular filtration rate in the three years of the study. Also, the development of macroalbuminuria was prevented in the patients with consistent microalbuminuria. These three studies point to the importance of early intervention in patients with diabetes and slight albuminuria. Increase in blood pressure further strengthens this indication, as recently shown by Lebovitz *et al*, who found that a fall in glomerular filtration rate was reduced in microalbuminuric patients by ACE inhibitors.³⁷

Overt diabetic renal disease

INSULIN DEPENDENT DIABETES MELLITUS
Antihypertensive treatment not only reduces albuminuria in patients with overt renal disease but also clearly reduces the rate of decline in glomerular filtration rate.⁸ The initial studies used a combination of β blockers and diuretics. Recent studies suggest that ACE inhibitors may have a more pronounced antiproteinuric effect. The most extended study on this subject, by Björck *et al*, finds that in advanced diabetic nephropathy ACE inhibitors are more efficient, not only in their antiproteinuric effect but also in reducing the rate of decline in glomerular filtration rate (fig 4).³⁸ Clearly, much of the effect of antihypertensive agents on the rate of decline in glomerular filtration rate in diabetic patients with nephropathy is related to the effect on blood pressure.³ The study by Björck *et al* suggests that an additional effect is obtained using ACE inhibitors, at least when combined with diuretics.³⁸ The superiority of ACE inhibitors was, however, not observed in all studies.³⁹

NON-INSULIN DEPENDENT DIABETES MELLITUS
Bakris *et al* studied patients with type 2 diabetes and clinical proteinuria.⁴⁰ Lisinopril and certain calcium blockers not only reduced proteinuria but also reduced the rate of fall in glomerular filtration rate.^{40 41} These studies were, however, fairly short term, with a maximal follow up of 1.5 years.⁴¹ Further studies are needed.

Patients with advanced renal disease

INSULIN DEPENDENT DIABETES MELLITUS
An interesting end point is the effect on the rate of decline in glomerular filtration rate. In one study captopril delayed the time to doubling of the serum creatinine concentration in patients with overt renal disease and insulin dependent diabetes (fig 5),⁴² reducing mortality and the need for dialysis or renal transplantation. ACE inhibitors were highly effective in reducing the blood pressure in these patients, and this may have accounted for much of the benefit. This is the first controlled study to document a significant effect on critical end points. Table 3 shows that ACE inhibition seems to be effective throughout the course of renal disease in

Table 3 Observations from clinical trials of ACE inhibition in patients with insulin dependent diabetes

Observation
No trials in patients with newly diagnosed disease
Normoalbuminuria reduced, blood pressure not significantly changed, filtration fraction reduced
Blood pressure reduced (diastolic and systolic), microalbuminuria reduced, fall in glomerular filtration rate prevented (8 year follow up)
Blood pressure reduced (diastolic and systolic), proteinuria reduced, rate of fall in glomerular filtration rate reduced
End stage renal disease and death postponed

Figure 4 Decline in glomerular filtration rate (GFR), urinary albumin excretion, and blood pressure before and during treatment with enalapril (●) or metoprolol (○) in 40 patients with insulin dependent diabetes and diabetic nephropathy.³⁸

insulin dependent diabetes mellitus. The effect is likely to be a class effect, rather than associated with a particular ACE inhibitor.

NON-INSULIN DEPENDENT DIABETES MELLITUS
A beneficial effect is also seen in some patients with type 2 diabetes, but the most convincing results are obtained in those with microalbuminuria. With more advanced disease structural vascular damage is probably more advanced,⁴³ and the efficacy of antihypertensive treatment may not be so pronounced. This emphasises the need for

Figure 5 Cumulative incidence of events in patients with diabetic nephropathy given captopril or placebo. Top: Cumulative percentage of patients with the primary end point: a doubling of the baseline serum creatinine concentration to at least 2.0 mg per 100 ml. Bottom: Cumulative percentage of patients who died or required dialysis or renal transplantation. The numbers refer to the numbers of patients in each group at risk for the event at baseline and after each six month period.⁴² Reprinted by permission of the "New England Journal of Medicine" (1993;329:1456-62).

screening patients with type 2 diabetes for microalbuminuria so that treatment is started early.

Possible mechanisms of the antiproteinuric effect of ACE inhibitors

The benefits of ACE inhibition are clear in animal studies, reducing proteinuria and structural glomerular damage in the rat model of diabetes.⁴⁴ The antiproteinuric and renal protective effect of ACE inhibitors probably operate through several mechanisms. A reduction in systemic blood pressure is important, reducing the transmission of the abnormal systemic pressure to the glomerular vessels. This may be especially important in diabetic patients, who may have disturbed autoregulation at the afferent arteriole.⁴⁵ Interestingly, filtration fraction is reduced by ACE inhibition,¹⁸ which probably reflects efferent arteriolar dilatation associated with a decrease in hydraulic glomerular pressure. Some studies suggest that there may be a direct effect on the permeability of the glomerulus,⁴⁶ but this may also be explained by decreased pressure induced stretch of the

glomerular vessels. If the hypothesis is correct that proteinuria in itself provokes renal damage by increased mesangial and interstitial flux of protein, a reduction in proteinuria would clearly be beneficial.⁴⁷ Inhibition of growth factors may also be operating. There are many other reports on the effects of ACE inhibitors on renal function and proteinuria, most of which, but not all, have shown benefit and broadly support one or more of the above hypotheses.⁴⁸⁻⁹⁰

When to start antihypertensive treatment in insulin dependent diabetes

The most recent studies suggest that antihypertensive treatment should be started in the microalbuminuric phase. This treatment should probably be introduced irrespective of blood pressure, but of course with low blood pressure a more conservative attitude should apply. Blood pressure usually increases without treatment during follow up. Some evidence suggests that glomerular filtration rate will remain well preserved if patients remain microalbuminuric or show reduction to normoalbuminuria. ACE inhibitors, often combined with small doses of diuretics, are then particularly useful with limited or no effect on glucose and lipid homeostasis. Triple treatment with diuretics, ACE inhibitors, and β_1 blockers also seems to be effective.²⁹⁻³⁰

Obviously, careful monitoring for changes in serum potassium concentration as well as glomerular filtration rate (serum creatinine concentration) is warranted, as well as careful control of blood pressure and monitoring of other side effects, especially in more advanced renal disease. Pregnancy or the desire for pregnancy is a clear contraindication for treatment.

The disease process is to some extent similar in the microalbuminuric and macroalbuminuric stages. Since preserving glomerular filtration rate is clearly beneficial in overt renal disease, similar benefits may be assumed among patients with microalbuminuria. This concept is supported by several studies. Importantly, the role of optimising diabetes control has recently been emphasised.¹¹ A low protein diet may also result in a beneficial effect on renal function.⁹¹

Brief suggestions for young and middle aged patients with type 2 diabetes

From a theoretical point of view the same guidelines can be used in patients with non-insulin dependent diabetes as for those with insulin dependent diabetes. Of course, higher blood pressures should be accepted to allow for the age dependent rise in pressure. Patients under 60 years old may be treated similarly to patients with insulin dependent diabetes after the effect of age on blood pressure has been taken into consideration.

So far there are no long term clinical trials in older patients. Experience indicates that ACE inhibition and conventional antihyper-

tensive treatment reduce blood pressure effectively in older patients with insulin dependent diabetes. Microalbuminuria may also be reduced, but there are no long term data that glomerular filtration rate is preserved. Generally, the guidelines for younger patients may be acceptable, but a higher blood pressure should be tolerated. If antihypertensive treatment reduces blood pressure and albuminuria with stable glomerular filtration rate, this is probably beneficial. Patients should be carefully monitored for hypotensive and other side effects, which are likely to be more prevalent in older people.

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