Effects of antihypertensive therapy on progression of diabetic nephropathy

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Effects of antihypertensive therapy on progression of diabetic nephropathy. There is a clear relationship between hypertension and the microvascular complications of diabetes. Genetic predisposition to hypertension has been correlated to the risk of diabetic nephropathy in type I diabetes, and hypertension is a well known risk factor for developing nephropathy in patients with type II diabetes. Multiple studies have emphasized the importance of hypertension on renal disease progression, and blood pressure control with conventional antihypertensive drugs slows the rate of renal function loss in diabetic nephropathy. Furthermore, evidence of the role of renin-angiotensin system (RAS) on progression of renal damage has focused much interest on the therapeutic action of the RAS blockade. In patients with type I diabetes, blocking the RAS with angiotensin converting enzyme (ACE) inhibitors prevents progression from microalbuminuria to overt nephropathy, and in overt nephropathy decreases the gradual loss of renal function beyond its blood pressure lowering effect. Less clinical information is available in type II diabetic nephropathy, but our experience and some recent studies suggest that ACE inhibitors also have a renoprotective action in type II diabetes. The role of calcium channel blockers in diabetic nephropathy is not clear. Several short-term studies with the first generation dihydropyridine calcium antagonists showed a lower effect on urinary albumin excretion and a more rapid progression to renal failure than with ACE inhibitors. However, other calcium channel blockers, particularly of the non-dihydropyridine type, have been shown to have a beneficial effect on diabetic nephropathy, decreasing proteinuria and slowing progression.

Diabetic nephropathy is currently the most important cause of end-stage renal disease in Western countries, mainly due to a gradual increase in the incidence of renal failure in patients with type II, non-insulin dependent diabetes mellitus (NIDDM) in recent years, particularly in the USA [1], but also somewhat later in European countries [2]. These data correct the previous erroneous estimate of the incidence of diabetic nephropathy in type II diabetes in the early eighties [3]. In fact, diabetic nephropathy can occur to the same extent with type I and type II diabetes, and almost 50% of patients with both types are at risk of developing overt nephropathy 25 years after the onset of the disease [4].

Diabetic nephropathy is a clinical syndrome characterized by the presence of persistent albuminuria (>300 mg/24 hr or 200 μg/min) associated with blood pressure elevation and a gradual decline in glomerular filtration rate. Some studies have shown that early increased excretion of urinary albumin, as measured by sensitive methods able to detect albuminuria below the levels from 15 to 200 (μg/min detected in conventional tests, the so-called microalbuminuria, clearly predicts progression to diabetic nephropathy in type I insulin-dependent diabetes mellitus (IDDM) [5] and less clearly in NIDDM patients [6].

The pathogenesis of diabetic nephropathy is not completely understood. Brenner and coworkers postulated a causal relationship between glomerular hypertension occurring in the earliest phase of the disease and glomerular damage in diabetic nephropathy [7, 8], and this “hemodynamic theory” has been confirmed by multiple experimental studies [9–13]. These hemodynamic changes and other non-hemodynamic factors related to chronic hyperglycemia, including sorbitol deposition, formation of glycosylation end-products with glomerular proteins and a number of vasoactive hormones, growth factors and cytokines, are important determinants in the development of diabetic nephropathy [14–17]. However, normalization of glomerular hypertension and control of systemic blood pressure appear to be essential to slow the progression of renal disease [18]. Several clinical studies have shown that blood pressure lowering with different types of antihypertensive drugs reduces the rate of decline of renal function in diabetic nephropathy [19–21], and more recent evidence in animal models and some controlled, prospective clinical trials, particularly in IDDM patients, suggests that there is an added renoprotective effect beyond its action on blood pressure when antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists are used [22–29]. However, clinical

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evidence of the beneficial effect of renin-angiotensin system (RAS) blockade in the progression of diabetic nephropathy is less convincing in type II diabetics [2].

GENETIC PREDISPOSITION TO HYPERTENSION AND DIABETIC NEPHROPATHY

There is some evidence that genetic predisposition to hypertension increases susceptibility to diabetic nephropathy [30]. In patients with type I diabetes, some authors have found that having a parent with hypertension increases the risk of nephropathy by almost four times compared to patients with no hypertensive parents [31]. Familial clustering of hypertension and cardiovascular complications is also well recognized in patients with type I [32] or type II diabetes with nephropathy [2], and a history of cardiovascular disease in parents also increases the risk of developing nephropathy.

Abnormalities of the Na\(^+\)/H\(^+\) exchanger, a marker of genetic predisposition to hypertension, have also been related to the risk of nephropathy, and some studies have demonstrated an increased activity of the Na\(^+\)/Li\(^+\) countertransport in red blood cells in patients with type I diabetes and nephropathy, as well as in their parents, compared to controls [31, 33]. This excess risk of renal disease associated with increased activity of the Na\(^+\)/Li\(^+\) countertransport in type I diabetic patients was mainly evident in patients with poor glycemic control during the first decade of diabetes [31]. However, this altered Na\(^+\)/Li\(^+\) countertransport activity in red blood cells of type I diabetic patients with nephropathy has not been found in all studies [34, 35].

Genes of the RAS have also been involved in the risk of nephropathy in IDDM. Nevertheless, this relationship of the insertion/deletion (I/D) polymorphism in the ACE gene to diabetic nephropathy [36] was not confirmed by all authors [37]. However, recent data suggest that type I diabetic patients who are homozygous for the D allele progress more rapidly to renal failure [38].

HYPERTENSION AS A RISK FACTOR IN DIABETIC NEPHROPATHY

High blood pressure is a common and early finding in diabetic nephropathy. In type I diabetes, blood pressure tends to increase slightly, concomitant with the onset of persistent microalbuminuria [39]. These changes in blood pressure may be detected even before transition to microalbuminuria occurs if ambulatory blood pressure monitoring is used. In normoalbuminuric IDDM patients, Poulsen et al found a clear positive relationship between ambulatory blood pressure and urinary albumin excretion as measured by RIA [40]. Attenuated circadian rhythm with reduced normal night drop in blood pressure has also been reported in diabetic patients. Using ambulatory blood pressure measurements, the prevalences of non-dippers (average reduction in systolic and diastolic blood pressure from day to night <10%) among type I diabetics with normoalbuminuria, microalbuminuria and overt nephropathy are 19%, 39% and 46%, compared to 10% of non-dippers among non-diabetic subjects [41]. The prevalences of non-dippers among elderly type II diabetics with normoalbuminuria, microalbuminuria and overt nephropathy increase to 42%, 50% and 58% respectively, as compared to only 14% of non-dippers in the non-diabetic control population [42].

In type II diabetes, hypertension, as a facet of the metabolic syndrome, is usually present for years before the appearance of nephropathy or even before the onset of diabetes. Hypertension is a frequent finding in type II diabetes, and its prevalence ranges from 50% to 70% of all patients with type II diabetes without proteinuria, increasing to 80% when proteinuria appears and to almost 100% in patients with type II diabetes and renal failure [2].

The presence of high blood pressure before the onset of diabetes is significant risk factor for the development of nephropathy in NIDDM [43]. However, in both types of diabetes hypertension enhances progression from microalbuminuria to overt nephropathy [44–45] and accelerates the rate of decline in renal function, thus increasing the prevalence and severity of hypertension in a vicious cycle leading to more advanced nephropathy [46–48].

Several studies have shown that hypertension is a strong progression factor for renal failure in diabetic nephropathy. Comparing the progression of renal failure in both types of diabetes, Biesenbach, Janko and Zazgomik found a more rapid progression in both type I and type II diabetics when systolic blood pressure was higher than 160 mm of Hg [46], and since the first observations of Danish authors showing that blood pressure control attenuates the gradual loss of renal function in diabetic nephropathy [19, 20], many others and some long-term studies have confirmed that in diabetic patients with proteinuria, lowering of systemic blood pressure with conventional antihypertensive drugs slows the rate of decline in renal function [49, 50].

ROLE OF THE RENIN-ANGIOTENSIN SYSTEM IN PROGRESSION OF DIABETIC NEPHROPATHY

Experimental studies in animals with diabetic kidney disease have shown that blockade of the RAS with ACE inhibitors or angiotensin II receptor antagonists preserves renal function [22–24], suggesting an essential role for intrarenal angiotensin II in the progression of renal damage in diabetic nephropathy. The importance of the RAS in the pathogenesis of diabetic nephropathy is suggested by multiple experimental and clinical studies [25]. Angiotensin II is a powerful vasoconstricting agent that acts not only by regulating systemic hemodynamics. Locally generated intraglomerular angiotensin II may cause constriction of mesangial cells and afferent–afferent arterioles, resulting in glomerular hypertension. In addition
to this glomerular hemodynamic action, angiotensin II also acts as a growth factor for renal cells, inducing the expression and renal synthesis of other autocrine factors and cytokines, including transforming growth factor beta (TGF-β1) [51], which in turn stimulates mesangial and epithelial cells and fibroblasts to produce extracellular matrix proteins and promotes fibrosis, thus contributing to progressive renal damage [25]. Angiotensin II also causes changes in the filtration properties of the glomerular basement membrane, increasing its permeability and aggravating proteinuria [53].

The significant role attributed to glomerular hypertension in the pathogenesis of diabetic nephropathy [8] suggested that RAS inhibition could be particularly useful in this condition. Apart from the beneficial antihypertensive effect, RAS blockade normalized glomerular capillary pressure as a result of the attenuation of the angiotensin II vasoconstrictive effect on glomerular efferent arterioles and inhibited all other non-hemodynamic angiotensin-mediated effects, resulting in a decrease in proteinuria and slowing progression [28].

Since the first report of Taguma, Kitamoto and Futaki showing a beneficial effect of captopril on proteinuria in nephrotic uremic diabetic patients [54], many other studies have documented the renoprotective benefits of ACE inhibitors to decrease urinary albumin excretion and to prevent the loss of renal function in IDDM patients with early and overt nephropathy, regardless of changes in blood pressure [28, 52]. However, evidence for the beneficial effect of ACE inhibition in type II diabetic nephropathy is not so convincing, owing to the absence of long-term, controlled clinical trials [2].

ANTIHYPERTENSIVE DRUG THERAPY PREVENTS PROGRESSION FROM MICROALBUMINURIA TO OVERT DIABETIC NEPHROPATHY

Based on this putative renoprotective effect of ACE inhibitors with no detectable changes in blood pressure, several investigators have examined the effect of ACE inhibitor therapy in normotensive IDDM patients with microalbuminuria. Viberti et al, on behalf of the European Multicenter Trial, clearly established that progression to clinical proteinuria is significantly less when normotensive IDDM patients are treated with captopril compared to a placebo [27]. The observation that ACE inhibitor therapy delays the development of diabetic nephropathy in normotensive IDDM with persistent microalbuminuria has been confirmed in several studies [52, 55, 57], and also in both IDDM and NIDDM diabetic patients with early nephropathy and hypertension [58–61]. In patients with early diabetic nephropathy, treatment with ACE inhibitors tends to slightly decrease glomerular filtration rate and filtration fraction, particularly in hyperfiltering patients [52].

As opposed to ACE inhibitors, the use of calcium channel blockers in early diabetic nephropathy is less well defined. Calcium antagonists inhibit the vasoconstrictive effect of angiotensin II through the blockade of calcium-dependent mechanisms, but their ability to reduce urinary albumin excretion and to preserve renal function has been questioned due to the vasodilation effect on afferent arterioles, which impedes reduction of intraglomerular pressure in spite of systemic blood pressure control [62]. Furthermore, experimental studies have shown that dihydpyridine calcium channel blockers, such as nifedipine, do not prevent the development of glomerulosclerosis due to their inhibitory action on renal self-regulation [63–65]. However, these drugs may also have other beneficial effects on renal damage mediated by mechanisms unrelated to their blood pressure lowering effects. Calcium channel blockers have been shown to reduce mesangial uptake of macromolecules induced by angiotensin II [66], and to inhibit mesangial cell proliferation [67].

The effect of nifedipine on microalbuminuric, normotensive type I (IDDM) diabetes was studied by Schnack et al in a randomized, double-blind trial, showing that treatment with nifedipine for a year significantly decreases urinary albumin excretion and glomerular filtration rate compared to placebo [68]. In both type I and type II patients, The Melbourne Diabetic Nephropathy Study compared nifedipine and perindopril in normotensive and hypertensive diabetic patients with microalbuminuria, and showed that a 12-month treatment with both drugs significantly decreased blood pressure and albuminuria in hypertensive microalbuminuric patients, while in normotensive patients there was no significant reduction in albuminuria with either regimen [58].

Agardh et al compared nifedipine with the ACE inhibitor lisinopril in a double-blind, randomized, parallel and multicenter 12-month trial with 335 hypertensive type II diabetic patients with early nephropathy [59]. These authors clearly demonstrated that treatment with lisinopril has a significantly greater beneficial effect on albuminuria than nifedipine, despite similar effects on ambulatory blood pressure. In this study there was no change in the glomerular filtration rate during either treatment [59]. However, several authors using another dihydpyridine calcium channel blocker, nitrendipine, in type I and type II diabetic hypertensive patients with early diabetic nephropathy have found a 17% to 44% increase in glomerular filtration rate associated with a significant decrease in albuminuria [60, 61, 69, 70].

ANTIHYPERTENSIVE TREATMENT IN OVERT DIABETIC NEPHROPATHY

There is large body of evidence in the literature demonstrating that blood pressure lowering decreases proteinuria and reduces the rate of decline of renal function in diabetic nephropathy secondary to type I diabetes, particularly when ACE inhibitors are used [20, 28, 49, 71].

The most complete clinical trial of the effects of ACE
inhibitors on overt diabetic nephropathy was reported by Lewis et al on behalf of the Collaborative Study Group in 1993 [28]. In this study, 409 patients with insulin-dependent diabetes, clinical proteinuria (>500 mg/dl) and serum creatinine <2.5 mg/dl were randomized to receive captopril or placebo during a median follow-up of 2.7 years. ACE inhibition treatment in this study led to decreased proteinuria and to a 50% reduction in the risk for doubling serum creatinine, dialysis and death. The risk reduction associated with captopril treatment was not significantly different in hypertensive compared to normotensive patients, and after adjusting for blood pressure during the treatment period, the lesser progression found in the captopril group was independent of the effect on systemic blood pressure [28].

Evidence for this beneficial effect of ACE inhibitors on progression is less compelling in type II diabetic nephropathy. Bakris et al compared the effects of the ACE inhibitor lisinopril with a non-dihydropyridine calcium channel blocker, diltiazem or verapamil, and atenolol during a six-year follow-up study on 52 NIDDM patients with diabetic nephropathy and hypertension, and found that urinary protein excretion was reduced with lisinopril and verapamil or diltiazem, but not with atenolol, despite similar levels of blood pressure control. The mean rate of decline of creatinine clearance was −0.98 ± 0.44 in the lisinopril group, −1.44 ± 0.63 in the non-dihydropyridine calcium antagonists group, and −3.48 ± 1.1 ml/min/year/1.73 m² in the atenolol group [72].

We have studied 91 NIDDM patients with diabetic clinical nephropathy. They all had clinical proteinuria >500 mg/dl and moderate renal failure (Ccr 25–70 ml/min). Fifty-seven of them were treated with ACE inhibitors and the other 34 patients with dihydropyridine calcium channel blockers during a follow-up period of two years. Target blood pressure levels were a systolic blood pressure below 140 mm Hg and a diastolic blood pressure below 90 mm Hg. Other drugs different from calcium antagonists or ACE inhibitors, respectively, were added when required to control hypertension in each group of patients. No previous differences were found in each group with regards to age, creatinine clearance or proteinuria, but systolic and diastolic blood pressures were higher in the ACE inhibitor group, since a drug of this class was given to patients with uncontrolled blood pressure before the start of the study, and only those patients with controlled blood pressure on calcium antagonists were maintained in this group (Table 1).

The primary end point of this study was the need for dialysis/transplantation or death. The average follow up was 22 ± 6 months, and 14 patients reached the primary end point; 11 patients showed end-stage renal disease (4 in the ACE inhibitor group and 7 in the calcium antagonist group) and 3 patients died during the study. One died from cardiovascular disease in the ACE inhibitor group and two patients died in the calcium antagonist group (one cardiovascular death and one infectious death). The rate of decline in creatinine clearance was 0.6 ml/min/month in the ACE inhibitor group, compared to 0.95 ml/min/month in the calcium channel blocker group. The median urinary protein excretion decreased −25% in the ACE inhibitor group, compared to a 49% increase in patients on calcium antagonists (Table 2).

Conversely, the effect of calcium channel blockers on renal function in overt diabetic nephropathy is not clearly determined. Some studies have shown that non-dihydropyridine calcium antagonists (diltiazem and verapamil) appear to have similar efficacy in controlling blood pressure, reducing proteinuria and slowing the rate of decline in renal function [72–74]. However, most studies conducted with the first generation dihydropyridine calcium channel blocker nifedipine show an increased progression of renal failure in spite of blood pressure control [75–77].

In a meta-regression analysis of 100 studies, Kasiski et al found that only ACE inhibitors were able to reduce the level of proteinuria and slow the rate of decline in renal function regardless of changes in blood pressure [29], and Weidmann et al, in a recent meta-analysis of the effects of different antihypertensive drugs on renal function in type I and type II diabetic patients with clinical nephropathy, showed a significantly lower progression with ACE inhibitor therapy than with conventional antihypertensive drugs (diuretics and/or beta blockers) or nifedipine. In this meta-analysis, some conflicting data emerged in analyzing the effects of different calcium antagonists. In five studies including only 63 patients with a median follow-up of 16.9 months, treatment with calcium antagonists other than nifedipine was associated to a 42% decrease in proteinuria and to a 2% increase in GFR per year. However, the number of cases treated with calcium antagonists other than nifedipine was too small to allow a clear interpretation of this possibly beneficial effect (Table 3) [77].

As suggested above, there is clear evidence that treatment with ACE inhibitors slows the progression of diabetic nephropathy beyond their effect on blood pressure, and

### Table 1. Type II diabetes and clinical nephropathy

<table>
<thead>
<tr>
<th>Age</th>
<th>ACE inhibitors</th>
<th>Calcium antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance ml/min</td>
<td>64.6 ± 8.1</td>
<td>68.4 ± 9.2</td>
</tr>
<tr>
<td>Proteinuria g/day</td>
<td>44.2 ± 2.2</td>
<td>43.4 ± 1.7</td>
</tr>
<tr>
<td>HDL mg/dl</td>
<td>3.9 ± 3.1</td>
<td>4.1 ± 3.3</td>
</tr>
<tr>
<td>LDL mg/dl</td>
<td>46 ± 11</td>
<td>43 ± 12</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>170 ± 46 a</td>
<td>147 ± 35</td>
</tr>
<tr>
<td>DBP mm Hg</td>
<td>160 ± 24 a</td>
<td>149 ± 18</td>
</tr>
</tbody>
</table>

Comparative data before the start of the study, between patients on ACE inhibitors and those on dihydropyridine calcium antagonists. Mean ± sd. Abbreviations are: HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*aP < 0.05
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Table 2. Effects of angiotensin converting enzyme (ACE) inhibitors and dihydropyridine calcium antagonists in patients with type II (NIDDM) and clinical nephropathy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up months</th>
<th>% Change in proteinuria</th>
<th>% Change in GFR</th>
<th>% Change in MBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (244)</td>
<td>21.2 (10.5–31.9)</td>
<td>39 (−7/85)</td>
<td>−0.7 (−1.3/0.0)</td>
<td>−2 (−9/5)</td>
</tr>
<tr>
<td>Diuretics and/or Beta-blockers (213)</td>
<td>16.5 (8.3–24.7)</td>
<td>−20 (−30/−10)</td>
<td>−0.8 (−1.6/0.1)</td>
<td>−10 (−12/−8)</td>
</tr>
<tr>
<td>ACE inhibitors (489)</td>
<td>9.5 (5.0–14.1)</td>
<td>−53 (−93/−14)</td>
<td>−0.1 (−1.3/1.1)</td>
<td>−16 (−31/−2)</td>
</tr>
<tr>
<td>Ca antagonists except nifedipine (63)</td>
<td>16.9 (1.9–35.7)</td>
<td>−42 (−64/−20)</td>
<td>0.2 (−0.6/0.9)</td>
<td>−16 (−23/−10)</td>
</tr>
<tr>
<td>Nifedipine (75)</td>
<td>8.0 (3.1–12.8)</td>
<td>−2 (−21/16)</td>
<td>−4.0 (−7.4/−0.7)</td>
<td>−12 (−16/−8)</td>
</tr>
</tbody>
</table>

From the meta-analysis of Weidmann et al [77]. Reprinted with permission from Nephrology Dialysis and Transplantation.

CONCLUSIONS

Hypertension is a risk factor for developing diabetic nephropathy, and also a strong progression factor for renal failure contributing to other diabetic complications, including heart and vascular atherosclerotic disease. Since high blood pressure clearly worsens the prognosis in diabetic patients with nephropathy, this strong risk factor must be strictly controlled. Some recent studies have demonstrated that progression from microalbuminuria to clinical proteinuria could be delayed if microalbuminuric type I diabetic patients are treated with ACE inhibitors. This evidence promotes prevention programs for the detection of microalbuminuria from the earliest phase of diabetes, particularly in patients with type I diabetes. Diabetic patients at risk should participate in intervention programs for blood pressure control, and if microalbuminuria occurs, administration of an ACE inhibitor even in the presence of normal systemic blood pressure values may prevent progression from microalbuminuria to overt nephropathy. Furthermore, there is strong evidence indicating that in type I diabetic patients with overt nephropathy, antihypertensive treatment with ACE inhibitors decreases proteinuria and slows progression to renal failure beyond their effect on blood pressure. Although in type II diabetes the clinical evidence of the advantage of ACE inhibitors over other antihypertensive drugs with regards to the progression of nephropathy is not as convincing, some recent studies and
our own experience suggest that antihypertensive treatment with ACE inhibitors in NIDDM patients also has more favorable effects on renal disease progression. Factors different from an effective blood pressure control that must be considered when treating diabetic patients with hypertension are the lack of adverse effects on metabolic control. ACE inhibitors, probably angiotensin II receptor antagonists and certain calcium channel blockers, particularly the non-dihydropyridine type, do not have a negative effect on glucose and lipid metabolism added to their renoprotective effect. This suggests that ACE inhibitors and non-dihydropyridine calcium channel blockers can be used as first-line antihypertensive drugs in diabetic patients with nephropathy. It is unknown whether a combination therapy of both types of drugs offers any advantages in slowing the rate of decline in renal function. The beneficial effect of angiotensin II receptor antagonists on progression of renal failure in diabetic nephropathy needs to be confirmed in long-term clinical studies.

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