*Review*

# Renoprotection in diabetes: genetic and non-genetic risk factors and treatment*

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Persistent albuminuria ( > 300 mg/24 h or 200 μg/min) is the hallmark of diabetic nephropathy, which can be diagnosed in the presence of diabetic retinopathy but absence of any clinical or laboratory evidence of other kidney or renal tract disease [1–3]. This definition is valid in patients with either Type II (non-insulin-dependent diabetes mellitus) or Type I diabetes (insulin-dependent diabetes mellitus) [3]. The clinical syndrome termed diabetic nephropathy is characterised by persistent albuminuria, early arterial blood pressure elevation, a relentless decline in glomerular filtration rate (GFR), and high risk of cardiovascular morbidity and mortality [3]. Previous studies have found a cumulative incidence of diabetic nephropathy of 25–40 % after a diabetes duration of at least 25 years in both Type I and Type II [4–9]. If strict metabolic control was achieved (mean $HbA_{1c} = 7.2$) less than 10 % of Type I patients diagnosed before the age of 15 years developed diabetic nephropathy [10]. This is, however, seldom the case and, consequently, diabetic nephropathy has become the leading cause (25–35 %) of end stage renal disease in Europe, the United States and Japan [3]. Unfortunately, the proportion of end stage renal disease (ESRD) patients suffering from diabetes, particularly Type II, is expected to rise considerably because the number of diabetic patients in the world is expected to double within the next 15 years, and because the individual diabetic patient lives longer and therefore is at a greater risk of developing late complications including diabetic nephropathy. The cost of care for ESRD in the United States currently exceeds 2.2 billion a year for diabetic nephropathy alone and the number is rapidly rising. In Europe the direct economic cost of diabetes is approximately 8–10 % of the health care budget and nearly 80–90 % of the direct cost is needed for the treatment of diabetic micro- and macroangiopathy [11]. Furthermore, it should be stressed that the indirect cost (economic loss due to disability and premature death from diabetes) is even greater than the direct expenses. Before the availability of advanced renal replacement strategies and antihypertensive therapy death occurred 5 to 10 years after the start of persistent proteinuria [4, 5, 12].

In this review I will discuss putative genetic and non-genetic progression promoters (risk factors for loosing filtration power) and summarise and analyse the evidence of the benefits of blood pressure lowering therapy and near-normal blood glucose control on the development and progression of diabetic nephropathy. A beneficial effect on kidney function (and structure) above and beyond that expected from the blood pressure-lowering effect alone is defined as renoprotection.

**Table 1.** Putative progression promoters in diabetic nephropathy

| |
| --- |
| Systemic blood pressure |
| Glomerular hypertension |
| Proteinuria |
| Glycaemic control |
| Hyperlipidemia |
| Dietary protein intake |
| Smoking |
| Oligonephropathy |
| ACE ID polymorphism |

## Progression promoters in diabetic nephropathy

*Systemic and glomerular hypertension.* A relentless but highly variable rate of decline in GFR (0–24 ml · min$^{-1}$ · year$^{-1}$) is found in both Type I and Type II with nephropathy [13–18]. Understanding the factors responsible for this variation in progression, i. e. identification of progression promoters, would help to direct future treatments (Table 1).

Increase in arterial blood pressure (BP) is an early and frequent phenomenon in diabetic nephropathy [19–21]. The association between systemic BP and decline in GFR was originally suggested by Mogensen [13] who found that diastolic BP at the end of follow-up correlated with the decline in GFR in preceding years and before onset of antihypertensive treatment. Two other studies of the natural history of diabetic nephropathy did not confirm this finding but numbers of study subjects were small in all three studies [14, 15]. In a larger prospective study of the natural history of diabetic nephropathy lasting 3 years we showed a significant correlation both in uni- and multivariate analysis [22]. A close correlation between BP and the rate of decline in GFR has been documented in Type I and Type II patients [23–26]. This suggests that increasing systemic blood pressure accelerates the progression of diabetic nephropathy. Previously, the adverse impact of systemic hypertension on renal function and structure was thought to be mediated through vasoconstriction and arteriolar nephrosclerosis [27]. Evidence from rat models shows though that systemic hypertension is transmitted to the single glomerulus in such a way as to lead to hyperperfusion and increased capillary pressure [28, 29]. Intraglomerular hypertension has also been documented in streptozotocin diabetic rats [28, 30].

Originally, Hostetter et al. [28] advocated the concept that increased glomerular hydraulic pressure plays an important role in the initiation and progression of diabetic glomerulopathy. Later treatment trials with blood pressure lowering drugs have confirmed their concept as discussed below. Finally, it should be recalled that elevated BP acts as a progression promoter in a variety of non-diabetic nephropathies as demonstrated in the modification of diet in renal disease study (MDRD) study, an investigation of 840 patients for a mean follow up period of 2.2 years [31].

*Proteinuria.* Proteinuria is generally regarded as a marker of the extent of glomerular damage but recent studies in various experimental animal models and human disease suggest that proteinuria itself may contribute to renal damage [32]. The worst prognosis has been shown in Type I patients with diabetic nephropathy and nephrotic range proteinuria ( > 3 g/ 24 h) [33]. We have confirmed and extended this finding to the early stages of diabetic nephropathy [22]. The patient belonging to the lowest tertiles of albuminuria (< 423 µg/min) had a rate of decline in GFR (ml · min$^{-1}$ · year$^{-1}$) of 3.8 compared with 9.0 in the highest tertiles (albuminuria > 2076 µg/min). Since then several observational studies and treatment trials have confirmed the above mentioned findings [23, 26, 34, 35]. Furthermore, intervention that has ameliorated the progression of diabetic renal disease has always been associated with a reduction in proteinuria (surrogate end point). The MDRD study [31] and the Ramipril Efficacy in Nephropathy (REIN) study [36] have demonstrated that proteinuria has a major impact on loosing filtration power in non-diabetic glomerulopathies.

*Glycemic control.* For many years it was believed that once albuminuria had become persistent, metabolic control had lost its beneficial impact on kidney function and structure, the concept of 'point of no return' advocated by many investigators [14, 15, 37, 38]. This misconception was based on studies with few patients applying inappropriate methods for monitoring kidney function (serum creatinine) and glycaemic control (random blood glucose). Originally, Nyberg et al. [39] demonstrated a correlation between HbA$_{1c}$ and rate of decline in GFR in 18 Type I patients receiving aggressive antihypertensive treatment for 18 months. Our 10 year prospective study confirmed and extended this observation by demonstrating that variation in glycaemic control and albuminuria could explain 2/3 of the variation in the rate of decline in GFR in 18 Type I patients receiving aggressive treatment with angiotensin converting enzyme inhibition (ACEI) [34]. In agreement with this several studies of large numbers of Type I patients have documented the important impact of glycaemic control on progression of diabetic nephropathy [25, 26, 40, 41]. In contrast most of the studies dealing with proteinuric Type II have failed to demonstrate any significant impact [16–18] with one exception [42].

Several metabolic pathways have been shown to play a role in glucose induced microvascular lesions, as reviewed by Porte et al. [43]. Furthermore, glucose induced apoptosis (programmed cell death) may also contribute by reducing functioning nephron numbers. [43 b]

## Hyperlipidemia

Originally it was advocated that hyperlipidaemia promotes progression in chronic kidney diseases once the initiating event has damaged the glomerular capillary wall thereby allowing increased passage of lipids, lipoproteins, and oxidized lipoproteins into the mesangium [44]. Hypercholesterolaemia may also induce raised glomerular capillary pressure by enhancing synthesis of vasodilating renal eicosanoids. Nearly all studies of Type I and Type II patients have shown a correlation between serum cholesterol concentration and progression of diabetic nephropathy at least in univariate analysis [16, 18, 24–26] although some have failed to demonstrate cholesterol as an independent risk factor in multiple regression analysis. Double blind randomised placebo controlled studies with statins in hypercholesterolaemic Type I [45, 46] and Type II [47] patients with elevated urinary albumin excretion have failed to show a beneficial effect on albuminuria (surrogate end point) and rate of decline in GFR (principal end point). Large double blind randomised placebo controlled clinical trials examining the effect of lipid lowering strategies on progression of diabetic and non-diabetic renal disease have, however, not been carried out.

*Dietary protein intake.* Dietary protein restriction retards the progression of renal disease in virtually every experimental animal model tested [27]. Suggested mechanisms for this protective effect include: reduction in glomerular hyperfiltration and glomerular capillary pressure, reduction in glomerular eicosanoid production (inducing vasoconstriction of the afferent arteriolar), reduction in proteinuria due to a protective effect on glomerular capillary permeability, reduction in hyperlipidaemia, and prevention of glomerular hypertrophy [27]. Surprisingly, all major observational studies of Type I and Type II patients with diabetic nephropathy have failed to show an impact of dietary protein intake on the rate of decline in GFR [16, 18, 24–26, 35, 37–41]. Although, a recent meta-analysis based on five studies of Type I patients [48–53] with microalbuminuria or overt proteinuria showed that a low-protein diet ( $< 0.8$ g $\cdot$ kg$^{-1}$ $\cdot$ day$^{-1}$) significantly slowed the increase in urinary albumin excretion rate or the decline in GFR or creatinine clearance (relative risk 0.56 [95 % CI 0.40 to 77]) [53]. Flaws in design (short-term non randomised crossover studies and self-controlled studies), methods (creatinine clearance) and insufficient adjustment for other progression promoters, including antihypertensive treatment with ACEI, have weakened the strength of the above mentioned conclusion [54]. Much more robust data are at hand in non-diabetic renal diseases [53].

*Smoking.* It has been suggested that smoking is an independent risk factor for the development of diabetic nephropathy in Type I patients [55]. This finding has been confirmed in numerous studies [56]. In addition, some, but not all, studies suggested that smoking can act as a progression promoter in both Type I and Type II patients with proteinuria [56, 57]. The renal mechanism involved is poorly understood but a significantly higher prevalence of glomerular hyperfiltration in smokers than in non-smokers with Type I has been reported [56]. We have shown that heavy smoking induces an abrupt rise in systolic BP and heart rate but vascular leakage of albumin, microalbuminuria and GFR are not altered in Type I patients [58]. Very little information is available concerning adverse effects of smoking on the evaluation and progression of other chronic renal diseases [56].

*Genetic risk factors.* Intrauterine growth retardation defined as birth weight below the 10th centile gives rise to a reduction in nephron number [59]. It has been suggested that oligonephropathy increases the risk of systemic and glomerular hypertension in adult life and enhances the risk of expression of renal disease following exposure to injurious renal stimuli e.g. diabetes mellitus [60]. Birth weight is known to vary directly with height. Adults with short stature (reduced height within the normal range) have an increased risk of developing diabetic nephropathy [61] and, among non-diabetic men, microalbuminuria [62]. We have shown there is an increased risk of diabetic nephropathy developing in Type I women who have suffered from intrauterine growth retardation [63]. In men we confirmed short stature is related to development of diabetic nephropathy [63]. These findings support the hypothesis that genetic predisposition or factors operating in utero or in early childhood or both contribute to the development of diabetic nephropathy. Thereafter we questioned whether low birth weight is a risk factor for progression of established diabetic nephropathy [64]. Our follow-up study for a median period of 9 (3–17) years of 114 Type I patients with nephropathy did not suggest that low birth weight is associated with an accelerated progression of diabetic nephropathy [64].

Increased synthesis of angiotensin II may play a role in the initiation and progression of diabetic nephropathy by affecting haemodynamic mechanisms and promoting growth of glomerular cells [3]. A recent study has shown that an insertion (I)/deletion (D) polymorphism of the ACE gene (ACE/ID) is strongly associated with the level of circulating ACE and increased risk of coronary heart disease in non-diabetic patients [65, 66]. The plasma ACE level in patients with the DD genotype is about twice that of patients with II genotype and those with the ID genotype have intermediate levels [66]. Following 168 proteinuric Type II patients for 10 years, analysis of the clinical course of the three ACE genotypes showed that the majority (95 %) of the patients with
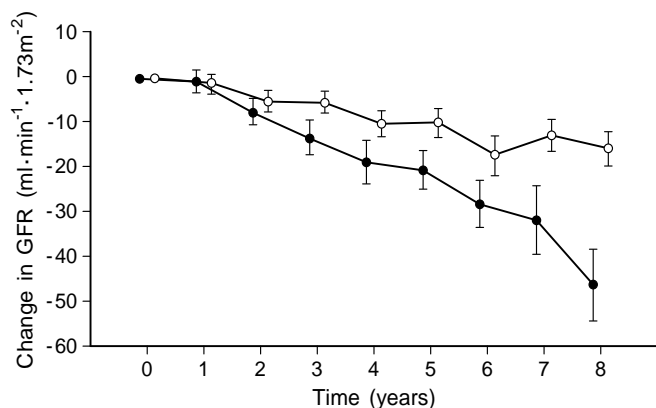
**Fig. 1.** Average change in the rate of decline in GFR during long-term angiotensin-converting enzyme inhibition frequently combined with diuretics in Type I patients with nephropathy, according to the I/D polymorphism of the angiotensin-converting enzyme gene ($p = 0.01$, DD (●) vs II + ID (○)). Parving et al. [70]

**Table 2.** Risk factors/markers for development of diabetic nephropathy in Type I and Type II patients

|  | Type I | Type II |
|---|---|---|
| Normoalbuminuria (above median) [77–79] | + | + |
| Microalbuminuria [80–86] | + | + |
| Sex [4,87–90] | M > F | M > F |
| Familial clustering [91–93] | + | + |
| Predisposition to arterial hypertension [94–98] | +/− | ? |
| Increased sodium/lithium counter transport [95–97, 99–102] | +/− | +/− |
| Ethnic conditions [103, 104] | + | + |
| Onset of Type I before 20 yrs [5, 20, 88] | + |  |
| Glycaemic control [105–107] | + | + |
| Hyperfiltration [35, 108–112] | +/− | ? |
| Prorenin [113–116] | + | ? |
| Smoking [55, 112, 118–121] | + | ? |
| Cholesterol [77, 78, 122] | + | + |
| Presence of retinopathy [16, 77, 78, 123] | + | + |

+, present; −, not present; ?, scanty or no relevant information

strated that the D allele is a risk factor for an accelerated course of diabetic nephropathy in Type I patients [71–74], although, in one of the studies the tendency towards a more rapid decline in kidney function in the DD genotype was non-significant [72]. Several studies in non-diabetic nephropathies, particularly IgA nephropathy, have clearly documented a deleterious effect of D allele on the course of the disease [75, 76].

## Prevention and treatment of diabetic nephropathy

The treatment strategies include: primary prevention, i.e. treatment modalities applied to any normoalbuminuric diabetic patient at risk; secondary prevention, i.e. treatment modalities applied to a diabetic patient with high risk (e.g. microalbuminuria) for development of diabetic nephropathy and finally, tertiary prevention, i.e. treatment of overt diabetic nephropathy.

*Primary prevention.* Risk factors for progression from normoalbuminuria to micro- and macroalbuminuria have been identified both in Type I and Type II patients as in Table 2 [4, 5, 16, 20, 35, 55, 77–123]. Despite the fact that patients with the highest absolute risk of progression can be identified, we still lack a large double blind randomised placebo controlled study with blood pressure lowering drugs e.g. ACEI or angiotensin II receptor blockers in such patients. In 1997 the EUCLID study group [124] performed a 2 year randomised placebo-controlled trial of Lisinopril in normotensive Type I patients ($n = 450$) with normoalbuminuria. The treatment difference was 12.7% (95% confidence interval (CI) –2.9 to 26), $p = 0.1$). Patients at a high absolute risk of progression to micro- and macroalbuminuria were not enrolled. On the contrary there have been several minor and major randomised trials comparing the effect of intensive treatment with conventional treatment on maintaining blood glucose concentrations close to the normal range.

A meta-analysis of all ($n = 7$) randomised studies [125] comparing the effect of intensive with conventional blood glucose control on risk of nephropathy progression in normo- and microalbuminuric Type I patients ($n = 266$) [126–132] showed that risk of nephropathy progression (defined as an increment in urinary albumin excretion) was decreased with intensified treatment (odds ratio 0.34 [0.20–0.58]) (Fig. 2). Most (approximately 80%) of the patients had normoalbuminuria ( < 30 mg/24 h) but microalbuminuric (30–300 mg/24 h) patients were enrolled in five out of the seven studies. Development of micro- and macroalbuminuria was not accounted for in the meta-analysis [125]. In the diabetes control and complication trial (DCCT) [133] however, intensive ther-

the DD genotype progressed to end stage renal disease (ESRD) within 10 years [67]. Moreover, the DD genotype appears to increase the mortality once dialysis is initiated. Two recent studies have confirmed that the D allele has a deleterious effect on kidney function [68, 69].

In a longitudinal study of GFR in Type I patients suffering from diabetic nephropathy we showed an accelerated initial and a sustained loss of GFR during ACEI in patients homozygous for the deletion polymorphism of the ACE gene [70]. The DD genotype independently influenced the sustained rate of decline in GFR or, in other words, acted as progression promoter (Fig. 1). Four other studies have demon-
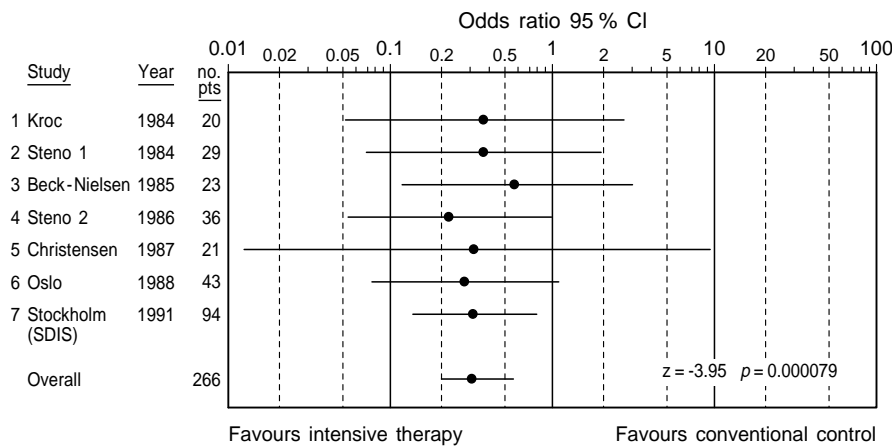
**Fig. 2.** Effects of intensive vs conventional blood glucose control on progression of nephropathy. Wang et al. [125], with permission
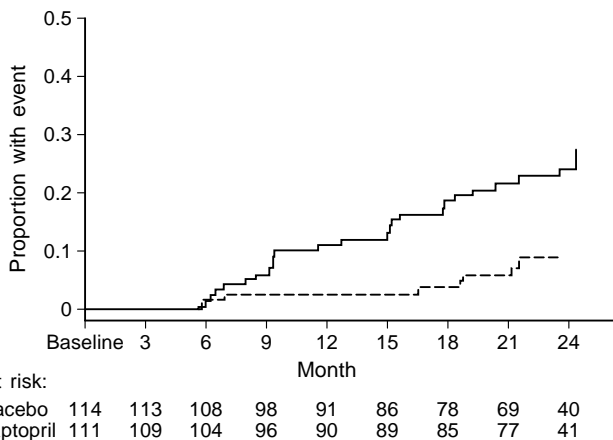


**Fig. 3.** Probability of progression to clinical albuminuria after treatment with captopril (- - -) or placebo (—) in Type I patients with microalbuminuria. Risk reduction: unadjusted = 69.2% (95% CI: 31.7–86.1%), p = 0.004. Adjusted for current mean arterial pressure (MAP) = 62.9% (16.1 to 83.6%), p = 0.017. Microalbuminuria Captopril Study Group [135], with permission

apy of Type I diabetes reduced the occurrence of microalbuminuria by 39% (95% CI, 21 to 52%), and that of albuminuria by 54% (95% CI, 19 to 74%), when analysing the two cohorts combined. Despite this, 16% in the primary prevention and 26% in the secondary prevention cohort developed microalbuminuria during the 9 years of intensive treatment. This clearly documents that we need additional treatment modalities in order to avoid or reduce the burden of diabetic nephropathy.

Finally, it should be recalled that a much smaller study, with a design similar to the DCCT, in Japanese Type II patients also showed a beneficial effect on progression of normoalbuminuria to micro- and macroalbuminuria [134].

*Secondary prevention.* Several modifiable risk factors (level of urinary albumin excretion, $HbA_{1c}$, BP, and serum cholesterol concentration) for progression from microalbuminuria to overt diabetic nephropathy have been identified in clinical trials of Type I and Type II patients [86, 135–138].

The beneficial effect of ACEI in preventing diabetic nephropathy was originally demonstrated in 20 normotensive Type II and Type I patients with persistent microalbuminuria [139, 140]. The study was double-blind for the first 6 months, single-blind for the last 6 months. Since then a large number of randomised open-labelled or double-blind placebo controlled ACEI trials, lasting from 2 to 8 years have been conducted in normotensive Type I patients with microalbuminuria [135, 141–143]. All these trials have confirmed and extended the evidence that ACEI postpones the development of diabetic nephropathy. In the largest trial of 235 microalbuminuric Type I patients only 7% developed nephropathy in the ACEI arm of the study while 21% in the group treated with placebo developed this complication (Fig. 3) [135]. Furthermore, rate of fall of creatinine clearance tended to be faster in the group treated with placebo than in the one treated with Captopril (6.4 vs 1.4 ml $\cdot$ min$^{-1}$ $\cdot$ 1.73 m$^{-2}$ $\cdot$ year$^{-1}$). Recently we showed that the beneficial effect of ACEI on preventing progression from microalbuminuria to overt diabetic nephropathy is long-lasting (8 years) and associated with preservation of normal GFR [144].

In the first long-term (5 years) double-blind randomised placebo controlled ACEI trial in normotensive microalbuminuric Type II patients 42% of the patients treated with placebo developed diabetic nephropathy compared with only 12% in the ACEI group [86]. Furthermore, serum creatinine concentration remained stable in the ACEI group while a significant raise occurred in the patients treated with placebo.

As to the renal impact of intensive diabetic treatment compared with conventional diabetic treatment on progression and regression of microalbuminuria in Type I patients (Table 3) five randomised studies

**Table 3.** Randomised studies comparing the renal effects of intensive (I) blood glucose control with conventional (C) treatment in Type I patients with microalbuminuria

| Study | Follow-up (years) | Baseline Number with microalbuminuria | End of study Normo-albuminuria | Micro-albuminuria | Nehphro-pathy | Change in urinary albumin excretion rate (%/year) | |
|---|---|---|---|---|---|---|---|
| DCCT [133] | | | | | | | |
| I | 6.5 | 38 | 23 | 11 | 4 | 2.5 | $p < 0.09$ |
| C | | 35 | 18 | 11 | 6 | 11 | |
| Stockholm study [145] | | | | | | | |
| I | 7.5 | 8 | 2 | 4 | 2 | −2.6 | $p = 0.04$ |
| C | | 13 | 4 | 5 | 4 | 11.8 | |
| Microalbuminuria Collaborative study, UK [146] | | | | | | | |
| I | 5 | 36 | 12 | 17 | 6 | | $p = 0.31$ |
| C | | 34 | 12 | 16 | 6 | | |
| Steno study [129] | | | | | | | |
| I | 2 | 18 | 3 | 15 | 0 | −9 | $p < 0.05$ |
| C | | 18 | 5 | 8 | 5 | 7 | |
| Oslo study [147] | | | | | | | |
| I | 2 | 9 | 4 | 4 | 1 | 10.8 | NS |
| C | | 9 | 1 | 7 | 1 | 5.8 | |
| All studies | | | | | | | |
| I | | 109[a] | 44 | 51 | 13 | | |
| C | | 109[a] | 40 | 47 | 22 | | |

[a] Chi-square test, $p = 0.26$ for distribution between the 3 groups, and $p = 0.15$ for progression to nephropathy

lasting from 2 to 7.5 years are available. At baseline the DCCT [133] and the Stockholm study [145] only measured urinary albumin excretion rate once and in the remaining three studies [129, 146, 147] patients were characterised based on urinary albumin excretion rate in the range of 30–300 mg/24 h in two of three urine specimens collected (persistent microalbuminuria). A beneficial effect of intensive treatment on rate of change in urinary albumin excretion rate was shown in three studies (borderline significant in the DCCT), while no significant changes were observed in the remaining two investigations [146, 147]. Analysing the impact on the categorical variable progression to diabetic nephropathy only one [129] study showed a beneficial impact of intensive diabetes treatment. The Microalbuminuria Collaborative Study Group failed to achieve prolonged glycaemic separation in the treatment groups for more than 3 years [146]. Analysis of all Type I diabetic patients enrolled in the five above mentioned intensive diabetic treatment trials (Table 3) showed no statistically significant impact on the distribution of normo-, micro-, and macroalbuminuria (chi square $p = 0.26$) and on progression to diabetic nephropathy (chi square $p = 0.1$). The small number of microalbuminuric Type II patients in the Japanese trial comparing conventional ($HbA_{1c}$ $9.4 \pm 1.5\%$) with intensive insulin ($HbA_{1c}$ $7.1 \pm 1.1\%$) therapy precludes a valid evaluation in relation to progression to diabetic nephropathy [134].

Reduction in GFR (10–15%) with improved glycaemic control is a well-established phenomenon [126, 128, 129]. This reduction per se will diminish urinary albumin excretion to the same degree. In order to adjust for this confounding influence of fluctuating GFR values, transglomerular albumin passage is expressed as the fractional albumin clearance, and calculated as: urinary albumin excretion · (GFR × plasma albumin concentration)$^{-1}$. Unfortunately, this correction is seldom applied in the primary and secondary prevention trials dealing with the impact of glycaemic control.

Recently, a consensus report on the detection, prevention, and treatment of diabetic nephropathy with special reference to microalbuminuria has been published [148]. Improved blood glucose control ($HbA_{1c}$ below 7.5–8%), and treatment with ACEI was recommended. This recommendation is very cost effective, mainly because ESRD treatment is so expensive [149]. From a therapeutic stand point, preventing the progression of kidney disease is more obtainable by a non-glycaemic intervention such as treatment with ACEI [146].

*Tertiary prevention.* As mentioned earlier, arterial hypertension, albuminuria, and poor glycaemic control act as the most important risk factors for loosing filtration power in diabetic nephropathy. Arterial hypertension is an early and frequent phenomenon in diabetic kidney disease [19–21], a state also characterised by a high prevalence of nocturnal hypertension ('non-dipping') [150, 151]. Furthermore, exercise induces a greater rise in systemic BP in long-term dia-
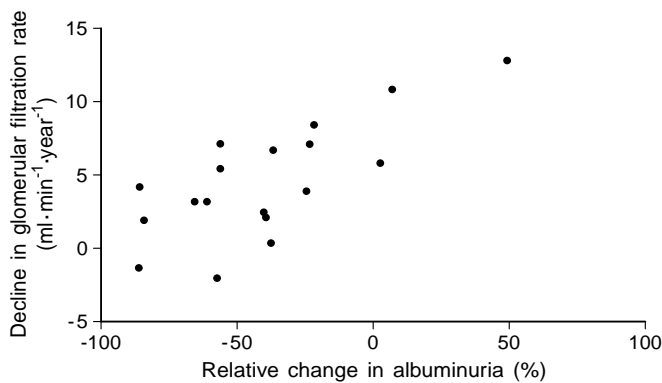
**Fig. 4.** Correlation between relative change in albuminuria and decline in glomerular filtration rate ($r = 0.73$ $p > 0.001$). Albuminuria was measured at baseline and during the first year after start of antihypertensive treatment, respectively. Glomerular filtration rate was measured for 3 years of antihypertensive treatment in 18 Type I patients with diabetic nephropathy. Rossing et al. [155], with permission

betic patients compared with non-diabetic control subjects [152]. Finally, impaired or abolished renal autoregulation or both [153, 154] will lead to enhanced transmission down stream of systemic BP inducing glomerular hypertension as can be shown in streptozotocin diabetic animals [28, 30]. The above mentioned finding could explain why the diabetic state has a special vulnerability to hypertensive injury.

From a clinical point of view the ability to predict long-term effect on kidney function of a recently initiated treatment modality, e. g. antihypertensive therapy, would be of great value since this could allow for early identification of patients in need of an intensified or alternative therapeutic regimen. In two prospective studies dealing with conventional antihypertensive treatment and ACEI we found that the initial reduction in albuminuria (surrogate end point) predicted a beneficial long-term treatment effect on the rate of decline in GFR in diabetic nephropathy (principal end point) [155, 156] (Fig. 4). These findings have been confirmed and extended [157, 158] and there have been similar findings in non-diabetic nephropathies [159, 160].

It should be stressed that the antiproteinuric effect of ACEI in patients with diabetic nephropathy varies considerably. Individual differences in the renin-angiotensin system may influence this variation. Therefore, we tested the potential role of an insertion (I)/deletion (D) polymorphism of the ACE gene on this early antiproteinuric responsiveness in an observational follow-up study of sixty young hypertensive Type I patients with diabetic nephropathy [161]. Our data showed that Type I patients with II genotype are particularly susceptible to commonly advocated renoprotective treatment. Recently, the Euclid Study Group [124] showed that urinary albumin excretion

rate was 57 % lower on lisinopril in the II group, 19 % lower in the ID group, and 19 % higher in the DD group compared with placebo. 530 normotensive Type I patients with normo- or microalbuminuria participated in this randomised double-blind trial lasting 2 years. Furthermore, the polymorphism of the ACE gene predicts therapeutic efficacy in ACEI against progression of nephropathy in Type II patients [162]. All previous studies in diabetic and non-diabetic nephropathies have shown that the deletion polymorphism of the ACE gene, particularly the homozygote DD, is a risk factor for an accelerated loss of kidney function [67–69, 71–76, 163]. Furthermore, the deletion polymorphism in the ACE gene reduces the long-term beneficial effect of ACE inhibition on progression of diabetic and non-diabetic kidney disease [70, 75]. These findings suggest that the DD genotype patient should possibly be offered more aggressive ACEI or treatment with the new angiotensin II receptor blockers.

Initiation of antihypertensive treatment usually induces an initial drop in GFR that is 3 to 5 times higher per unit of time than during the sustained treatment period [164]. This phenomenon occurs with any antihypertensive treatment, with β-blockers, and diuretics, and when ACE inhibitors are used. Whether this initial phenomenon is reversible (haemodynamic) or irreversible (structural damage) after prolonged antihypertensive treatment has recently been the subject of investigation. In Type I patients suffering from diabetic nephropathy, our results render some support to the hypothesis that the faster initial decline in GFR is due to a functional (haemodynamic) effect of antihypertensive treatment which does not attenuate over time and the subsequent slower decline reflects the beneficial effect on progression of nephropathy [165]. A similar effect has been demonstrated in non-diabetic glomerulopathies [166]. In contrast our results suggest that the faster initial decline in GFR after initiating antihypertensive therapy in hypertensive Type II patients with diabetic nephropathy is due to an irreversible effect [164].

Long-term antihypertensive treatment slows the rate of decline in GFR from 1.23 to 0.49 ml · min$^{-1}$ · month$^{-1}$ as shown originally in five hypertensive Type I men with nephropathy [13]. Our prospective study has demonstrated that early and aggressive antihypertensive treatment reduces albuminuria and the decline in GFR in young Type I men and women with diabetic nephropathy [1, 167, 168]. Figure 5 illustrates the mean value for arterial blood pressure, GFR, and albuminuria in nine patients receiving long-term ( > 9 years) treatment with Metoprolol, Furosemide and Hydralazine [168].

The first studies dealing with ACEI in Type I patients with nephropathy were published in 1986 [169, 170]. Both studies showed that GFR is not dependent on angiotensin II, ACEI reduces albuminuria (proba-
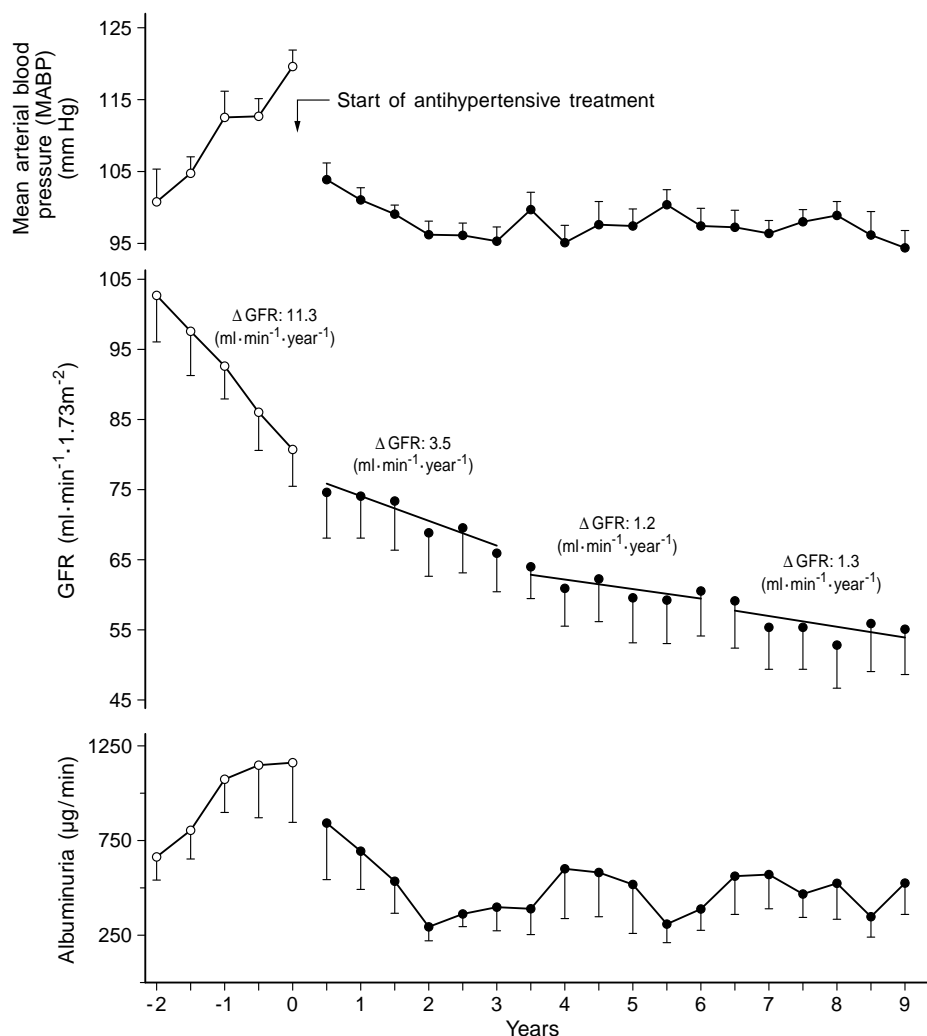
**Fig.5.** Average course of mean arterial blood pressure, GFR, and albumin before (○) and during (●) long-term effective antihypertensive treatment on nine Type I patients suffering from diabetic nephropathy. Parving et al. [34], with permission

bly by lowering glomerular hypertension) and inhibitors of ACE should be considered for lowering blood pressure in Type I patients with diabetic nephropathy. Furthermore, the beneficial effect of long-term ACEI on the progression of diabetic nephropathy was described [171]. However, the design of these original studies was not ideal because a patient self-controlled approach and a non-randomised before-after trial were carried out. In 1989, we reported the first randomised open-labelled follow-up study of normotensive Type I patients with nephropathy who had either been treated or not treated with Captopril for one year [172]. Thereby ACEI was shown to arrest the progressive rise in albuminuria; similarly antihypertensive treatment with Enalapril was shown to reduce proteinuria in Type I patients with diabetic nephropathy more than an equally effective antihypertensive treatment with Metoprolol [173].

Renoprotection – a beneficial effect on kidney function (and structure) above and beyond that expected from the blood pressure-lowering effect alone – was originally suggested for ACEI in diabetic nephropathy in a prospective, open randomised study lasting a mean of 2.2 years in Type I patients [173] (Fig. 6). Comparing the in a double-blind study effects of Captopril (25 mg 3 times daily) with placebo in normotensive and hypertensive (receiving conventional antihypertensive treatment, excluding calcium channel blockers) Type I patients with diabetic nephropathy [174], a non-significant risk reduction (33 %; 95 % CI; range, –44 % to 49 %; $p = 0.31$) was observed in the time-to-doubling of serum creatinine concentration in 307 patients with baseline creatinine below 133 μmol/l. In contrast, a significant risk reduction was seen in patients treated with Captopril (68; 95 % CI; range, 39 % to 63 %) whose baseline creatinine concentration was higher than 133 μmol/l. It was assumed that the effect was independent of blood pressure control. Unfortunately, several important cofounders such as blood pressure control, level of proteinuria, baseline creatinine clearance, and race were not sufficiently balanced between the patient groups
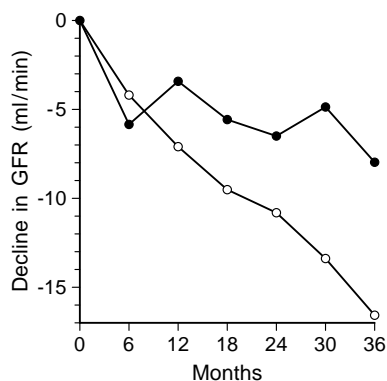
**Fig. 6.** Decline in GFR during treatment with enalapril (●) or metoprolol (○) in 40 Type I patients with diabetic nephropathy. Björck et al. [170], with permission

[175]. When these confounding variables, all favouring the Captopril group, are considered there is no way of knowing beyond reasonable doubt whether the reported differences are true and the results of a specific action by Captopril [175]. The rate of loss of GFR in the study by Lewis et al. [174] was astonishingly high (11 vs 17% per year for Captopril vs placebo with a mean baseline 24 h creatinine clearance of 84 and 79 ml/min) compared with results in most European and American trials [176]. This difference might be due to differences in patient selection and in the concomitant treatment. Furthermore, we still lack information on the impact of Captopril treatment compared with placebo in the 101 normotensive Type I patients with nephropathy included in the aforementioned trial [174]. Recently, we evaluated the long-term effect (8 years) of Captopril on kidney function in normotensive Type I patients with diabetic nephropathy [177]. Thirty-two Type I patients were randomly allocated between a Captopril (n = 15) and a control group (n = 17). Our study showed that the beneficial effect of Captopril in arresting the progressive rise in systemic blood pressure and albuminuria is long-lasting in normotensive Type I patients with nephropathy. Loss in GFR is minimal in most Type I patients with diabetic nephropathy when normotension is sustained.

Analysis of antihypertensive treatment with and without ACEI on albuminuria and on GFR in hypertensive Type II patients with proteinuria (Table 4) [178–181] demonstrates a greater antiproteinuric effect of ACEI compared with regimens not including ACEI. Except for one study [180] no significant difference was found between the decline in GFR in patients over time with or without ACE inhibition, but numbers are small. Consequently, large multinational, randomised placebo-controlled trials with angiotensin II receptor blockers are carried out in hypertensive Type II diabetes with proteinuria. In this context it should be recalled that a beneficial effect of antihypertensive treatment with and without ACEI has been documented in Type II patients with nephropathy [178–181].

The effect of ACEI on the progression of non-diabetic renal disease has been analysed in a meta-analysis of all 11 randomised trials available [182]. This analysis documented that ACEI is more effective than other antihypertensive agents in reducing the development of ESRD. It could not be determined whether this beneficial effect is due to the greater decline in arterial blood pressure or to other effects of ACE inhibition (renoprotection).

It has been suggested [183] that by the time glomerular function has started to fail in diabetic nephropathy the process culminating in ESRD has become self-perpetuating and is little influenced by the degree of metabolic control. This suggestion was based on a study of 12 Type I patients with nephropathy, 6 of whom received continuous subcutaneous insulin infusion for up to 24 months and maintained a $HbA_{1c}$ around 9.5% (normal range 5.5–8.5%). In the same year it was reported that diabetic glomerulosclerosis can be reversed after 7 months if affected kidneys are transplanted into non-diabetic patients [184]. Unfortunately, this has not been confirmed. On the contrary, diabetic glomerular lesions in patients with their own kidneys were not ameliorated by pancreas transplantation after 5 years of normoglycaemia [182] although diabetic glomerular lesions can be reversed after 10 years of normoglycaemia [185].

*Prognosis.* On average death occurs 5 to 10 years after the start of persistent proteinuria [4, 5, 12]. This information is based on the three studies reflecting the natural course of diabetic nephropathy. The 10 year figure is a maximum value as the study included only death due to ESRD [5]. The kidney prognosis in Type II patients with proteinuria is similar to that of the Type I patients [18].

Assessing the effect of long-term antihypertensive treatment on prognosis in diabetic nephropathy by

**Table 4.** ACEI in proteinuric Type II patients

| Investigator | N | Treatment | Follow-up (years) | Proteinuria | | | GFR $ml \cdot min^{-1} \cdot years^{-1}$ | |
|---|---|---|---|---|---|---|---|---|
| Walker [178] | 86 | ACEI vs conv.[a] | 3 | ↓↓ | | ↓ | 3.0 | 4.1 |
| Lebovitz [179] | 46 | ACEI vs conv.[a] | 3 | ↓ | | → | 6.4 | 9.6 |
| Bakris [180] | 52 | ACEI vs CCB vs BB | 5 | ↓↓ | ↓↓ | ↓ | 1.0 | 1.4 |
| Nielsen [181] | 36 | ACEI vs BB | 3 | ↓↓ | | → | 7.0 | 6.5 |

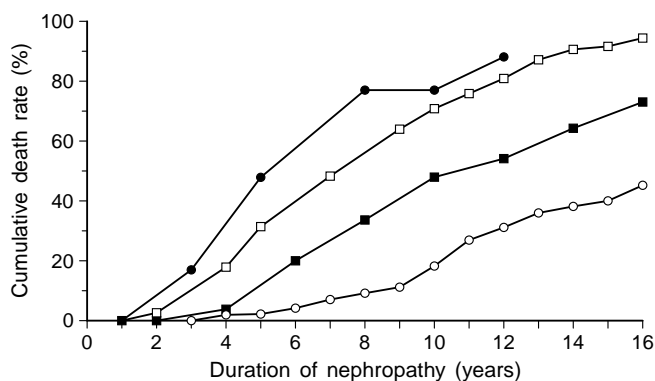[a] non-ACE inhibiting antihypertensive drugs

**Fig. 7.** Cumulative death rate during the natural history of diabetic nephropathy in Type I patients (×, *n* = 45, Knowles [12]; □, *n* = 360, Andersen et al. [4]; ■, *n* = 67, Krolewski et al. [5] compared with patients who had effective antihypertensive treatment, ○, *n* = 45, Parving et al. [188], with permission

studying prospectively all Type I patients (*n* = 45) (under 50 years with onset of diabetes before the age of 31 who developed diabetic nephropathy between 1974 and 1978 at Steno Diabetes Center) [186] the cumulative death rate was 18% (95% CI, 8 to 32%) 10 years after onset of nephropathy, in contrast to previous reports of 50% to 77% [4, 5, 12]. As in previous studies ESRD (defined as serum creatinine concentration above 500 μmol) was the main cause of death (64%). Survival of Type I with nephropathy has, however, improved substantially since the early use of effective antihypertensive treatment with conventional drugs has become routine [187]. Recently we extended the follow-up of our 45 patients with diabetic nephropathy until death or for at least 16 years (median 16 [4 to 21] years) [188]. The median survival time in our study exceeded 16 years (Fig. 7) and serum creatinine was 116 (74 to 311) μmol/l in the 23 surviving patients. These results were confirmed in another long-term observational follow-up study showing a median survival time of 13.9 years (95% CI 11.8 to 17.2 years) in 263 Type I patients suffering from diabetic nephropathy [163]. The study also showed that death due to ESRD (dying with serum creatinine concentration above 500 μmol/l) was reduced to 35%.

The first information on progression based on a randomised, double-blind placebo controlled antihypertensive treatment trial was presented by the Collaborative Study Group of Angiotensin Converting Enzyme Inhibition with Captopril in diabetic nephropathy [174]. The mean duration of the study was 2.7 years and risk reduction for the occurrence of death or progression to dialysis or transplantation 61% (95% CI 26 to 80%, *p* = 0.002) in the subgroup of 102 Type I patients with baseline serum creatinine concentration greater than 133 μmol/l, but 46% (*p* = 0.14) in the 307 patients with serum creatinine concentration at baseline below 133 μmol/l when treated with Captopril compared with placebo. An economic analysis of the use of Captopril in diabetic nephropathy showed ACEI will provide significant savings in the health care costs [189].

*Conclusion.* There appear to be no substantial differences between patients with Type II and those with Type I with respect to the initiation, progression, and treatment of diabetic nephropathy. What is more important is that modifiable risk factors including elevated blood pressure and proteinuria for both initiation and the progression of diabetic nephropathy have been identified. The natural course can be altered by antihypertensive drug therapy and tight glycaemic control [190].

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