Overt diabetic nephropathy (DN) is characterized by a large variation in the interindividual loss of GFR (0 to 24 ml/min per yr) and consequently time to doubling of s-creatinine and ESRD (1). Albuminuria, elevated BP, and poor metabolic control are established progression promoters (1), but these risk factors account for only approximately one third of the variability in loss of GFR (2). Identification of new risk factors for progression of DN is crucial to delay/prevent ESRD.

Systemic and local generation of angiotensin II is of major importance in the processes that initiate and eventually lead to loss of filtration power in DN (1). Therefore, genetic variations in the renin-angiotensin system (RAS) are potential risk factors for progression of DN.

Originally, we reported patients homozygous for the deletion (D) allele of a polymorphism in the gene coding for angiotensin-converting enzyme (ACE/ID) to have an accelerated loss of GFR during 7 yr of ACE inhibition (ACE-I) in 35 patients with type 1 diabetes and DN (3). Furthermore, in a prospective follow-up study of 56 patients with type 2 diabetes, the DD genotype was associated with increased loss of calculated creatinine clearance and increased 3-yr mortality (4). Other studies (5–10) did not find an effect of the D allele on progression of established DN; thus, the impact of the ACE/ID polymorphism is still controversial.

Variants in the genes coding for angiotensinogen (M235T) and for angiotensin II type 1 receptor (A1166>C) have been associated with hypertension in some studies (11–13). The role of these polymorphisms in relation to progression of diabetic nephropathy needs further investigation.

In a long-term observational follow-up study, we tested the impact of polymorphisms in the genes coding for angiotensinogen (M235T), ACE (ID), and angiotensin II type 1 receptor (A1166>C) on decline in GFR and time to doubling of s-creatinine or ESRD. We investigated all patients who had type 1 diabetes and overt DN and were treated with ACE-I at Steno Diabetes Center.

Materials and Methods

From the introduction of ACE-I treatment in 1985, we consecutively identified all adult patients who had type 1 diabetes with DN and were treated with ACE-I at Steno Diabetes Center. Patients had their GFR measured routinely once a year. Included in the present observational follow-up study were all albuminuric patients who were treated with ACE-I and had a follow-up period of at least 3 yr with three or more measurements of GFR (n = 169). The follow-up period ended on January 7, 2000.

DN was diagnosed clinically when the following criteria were fulfilled: persistent albuminuria >200 μg/min in two of three con-
secutive determinations, presence of diabetic retinopathy, and no other kidney or renal tract disease (1). We defined ESRD as the need for dialysis or renal transplantation and doubling of serum creatinine as an increase of 100% to >177 µmol/L, as suggested previously (14). All patients had been dependent on insulin treatment from the time of diagnosis (<40 yr of age) and received at least two daily injections of insulin. Patients were recommended a diabetic diet (45 to 55% carbohydrates, 30 to 35% fat, and 15 to 20% protein) without restriction in sodium or protein intake. The local ethical committee approved the experimental design, and all patients gave their informed consent.

Methods

Clinical and laboratory characteristics at baseline are based on the first GFR investigation on ACE-I treatment, and follow-up values are based on all data during ACE-I treatment for each patient. During follow-up, patients had their dose of insulin and antihypertensive treatment adjusted every 2 to 4 mo in the outpatient clinic. The dose of ACE-I is given as mean during follow-up. All types of ACE-I were converted to captopril equivalents; we defined 25 mg of captopril as equivalent to 5 mg of lisinopril/enalapril. With regard to non–ACE-I treatment, patients were classified as taking a class of antihypertensive agent when the drug was prescribed for >50% of their follow-up time.

The GFR was measured after a single intravenous injection of $^{51}$Cr-EDTA (3.7 MBq) at 08:30 a.m. by following the plasma clearance of the tracer for 4 h (15). The results were standardized for 1.73 m$^2$ body surface area, using the patient surface area at the initial GFR measurement. The intraindividual mean day-to-day coefficient of variation in GFR is 4% in our laboratory. Since 1991, urinary albumin excretion rate was determined during the 4-h clearance period by an enzyme immunosassay (16); before 1991, a RIA was used (17). The two methods are in close correlation ($r = 0.99$, linear regression equation: $\text{RIA} = 1.06 \times \text{ELISA}$) (16).

Arterial BP was measured with a standard clinical mercury sphygmomanometer, at least three times during each investigation after the patient had been supine for >10 min. Arterial hypertension was diagnosed according to World Health Organization criteria until 1995, and antihypertensive medication was prescribed when at least three consecutive recordings revealed a systolic BP >160 mmHg and/or a diastolic BP >95 mmHg. After 1995, the treatment strategy was intensified and the criteria from the American Diabetes Association (BP >140/90 mmHg) were used for the diagnosis of hypertension.

From venous blood samples, hemoglobin $A_1c$ (normal range, 4.1 to 6.4%) was determined at each investigation as described previously (18). Cholesterol concentration was measured enzymatically using CHOD-PAP reagents from Boehringer-Mannheim (Mannheim, Germany).

Genotyping was carried out on genomic DNA isolated from human leukocytes. The genotypes of angiotensinogen ($M235T$), ACE/ID, and angiotensin II type 1 receptor ($A^{1166}_I\rightarrow C$) polymorphisms were detected by PCR as described previously (18). In addition, a specific primer for the insertion allele was used to confirm ACE/ID genotypes. We were able to determine genotypes of angiotensinogen ($M235T$) and ACE/ID in all patients and the angiotensin II type 1 receptor ($A^{1166}_I\rightarrow C$) polymorphism in 168 of the 169 individuals.

Statistical Analyses

Linear regression analysis (least squares method) was used to determine the rate of decline in GFR for each patient, using all measured values during follow-up. Normally distributed variables, including logarithmically transformed values of albuminuria, were compared with an unpaired $t$ test or ANOVA test. Nonnormally distributed variables were compared with a Mann-Whitney $U$ or Kruskal-Wallis test. $\chi^2$ tests were made to compare proportions.

A multiple linear regression model with rate of decline in GFR as dependent variable and gene polymorphism in RAS and mean values during follow-up of well-known progression promoters in DN (albuminuria, mean BP, hemoglobin $A_1c$, and cholesterol) as independent variables was performed. To investigate the interaction between genetic polymorphisms and in an attempt to strengthen the statistical power of the analysis, we made a second model in which the three investigated gene polymorphisms were reduced to one genetic variable. The combined genetic variable consisted of the total number of potential “bad” alleles (range, 0 to 6) identified from the estimates of differences in decline in GFR within each polymorphism in the linear model, including all three genetic variants. In other words, the model identified genotypes with the potential fastest decline in GFR, although significant single-gene effects were not present. The estimated differences in decline in GFR within the three polymorphisms were compared to ensure equal contribution to the reduced genetic variable. Tests for independent distribution of the three polymorphisms were performed.

We made two Cox proportional hazards regression models (survival analysis) of baseline variables predicting time from onset of DN to doubling of s-creatinine or ESRD, one including the gene polymorphisms as separate variables and one with the total number of “bad” alleles as genetic component. Data were left truncated because not all patients were followed from onset of DN. Results are expressed as rate ratio with 95% confidence interval (CI). Kaplan-Meier estimates of survival curves were made for relevant groups. $P < 0.05$ (two sided) was considered to be significant. Linear models and survival analysis were made using the freely available software R (www.r-project.org). All other calculations were performed using SPSS 11.0 (SPSS, Chicago, IL).

Results

At baseline, patients with different RAS genotypes were comparable with respect to demographic variables (Table 1). The median daily dose of ACE-I was 50 mg of captopril (range, 12.5 to 200 mg/d). Seventy-eight percent of the patients received antihypertensive treatment in addition to ACE-I for the majority of the follow-up period. The median total number of drugs was two (range, 1 to 4). Loop diuretics were used in 66% of patients (median dose, 120 mg/d; range, 20 to 1000), bendrofluazide in 9% of patients, calcium channel blockers in 15%, $\beta$-blockers in 11%, and hydralazine in 8% of patients. None of the patients received angiotensin II receptor blockers for the majority of follow-up or for >3 yr; therefore, this treatment type did not influence disease progression in our study. We found no differences in ACE-I dose or other antihypertensive therapy between patients with different RAS genotypes. Genotype proportions were in Hardy-Weinberg equilibrium, and the polymorphisms were independently distributed.

During the 6 yr (range, 3 to 15 yr) of follow-up, GFR and other physiologic investigations were carried out nine (range, three to 29) times. The median (range) rate of decline in GFR was 3.1 ml/min per yr (=−2.3 to 27.3 ml/min per yr). The SD of residuals in linear regression of decline in GFR in each patient was (median [interquartile range]), 5.4 ml/min per yr [3.9 to
Baseline clinical and laboratory data in 169 patients with type 1 diabetes and diabetic nephropathy treated with ACE-I according to RAS polymorphisms

<table>
<thead>
<tr>
<th>Table 1.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE (I/D)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MM (n/H11005)</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>40/20</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Diabetes duration (yr)</td>
<td>26 (8)</td>
</tr>
<tr>
<td>Duration of nephropathy (yr)</td>
<td>4 (1 to 7)</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m²)</td>
<td>84 (29)</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>141 (23)/85 (11)</td>
</tr>
<tr>
<td>Albuminuria (g/min)</td>
<td>473 (337 to 666)</td>
</tr>
<tr>
<td>Hemoglobin A₁C (%)</td>
<td>9.2 (1.6)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.8 (1.3)</td>
</tr>
</tbody>
</table>

*ACE-I, angiotensin-converting enzyme inhibitor; RAS, renin-angiotensin system. Values are means (SD).*  
*Median (interquartile range).*  
*Geometric mean with 95% CI.*  
*NS comparing groups within each gene polymorphism.*

---

8.0 ml/min per yr). This estimates the absolute deviation from regression line in each individual. Forty-nine patients doubled their serum creatinine (29%) and 23 (14%) reached ESRD during follow-up. The median time from onset of DN until ESRD was 12 yr (range, 5 to 19 yr).

The Cox proportional hazards regression model revealed that the following baseline variables influenced time to doubling of s-creatinine or ESRD during ACE-I: GFR level (rate ratio, 0.99 per 1 ml/min per 1.73 m²; 95% CI, 0.98 to 1.00; P = 0.014), albuminuria (rate ratio, 2.08 per 10-fold increase in albuminuria; 1.03 to 4.18; P = 0.041), hemoglobin A₁C (rate ratio, 1.25 per 1%; 1.05 to 1.49; P = 0.012), cholesterol (rate ratio, 1.31 per 1 mmol/L; 1.04 to 1.65; P = 0.025) and number of D alleles (rate ratio, 1.81 per allele; 1.09 to 3.03; P = 0.023).

Kaplan-Meier estimates of survival curves in patients with different ACE/ID genotype are shown in Figure 1. In the linear model including all three genetic polymorphisms as separate variables, none of them had significant influence on decline in GFR (Table 2). For all differences in rate of decline in GFR between genotypes, we found 95% CI with limits up to approximately 2 ml/min per yr. However, the analysis identified M235T, A1166C and D1366C alleles as the potential “bad” alleles, despite the lack of significant single-gene effects on GFR.

In an attempt to analyze genetic interaction and to strengthen statistical power, we calculated total number of M/D/A alleles for each patient (0 alleles, 0 pts; 1, 1 pt; 2, 19 pts; 3, 53 pts; 4, 58 pts; 5, 28 pts; 6, 9 pts; see Table 3) and introduced into the linear model as the only genetic component. The distribution of number of “bad alleles” was as expected based on the present and previous reported allele frequencies (see the Discussion section). The analysis revealed the following variables to be associated with accelerated decline in GFR during ACE-I: albuminuria (estimate, 2.12 ml/min per yr per 10-fold increase in albuminuria; 95% CI, 1.06 to 3.18; P = 0.001), mean BP

---

Figure 1. Kaplan-Meier estimation of time to doubling of s-creatinine or ESRD according to number of D alleles of the ACE/ID polymorphism (left truncated from onset of nephropathy to start of follow-up).  
- - - - patients with II genotype; ----- ID patients; · · · · patients with DD genotype. Vertical bars represent standard errors. Rate ratio 1.81 per allele (95% confidence interval [CI] 1.09 to 3.03; P = 0.023) in Cox proportional hazards model correcting for other risk factors [see text].
Table 2. Clinical and biochemical variables during 6 yr of follow-up in 169 patients with type 1 diabetes and diabetic nephropathy treated with ACE-I in relation to RAS polymorphisms

<table>
<thead>
<tr>
<th>RAS Polymorphisms</th>
<th>ACE/DD</th>
<th>ACE/MM</th>
<th>ACE/TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>M235T/D1166C/ID/A</td>
<td>3.3 (1.8 to 6.0)</td>
<td>2.8 (1.3 to 5.9)</td>
<td>3.0 (1.5 to 6.0)</td>
</tr>
<tr>
<td>Angiotensinogen</td>
<td>3.1 (1.8 to 5.4)</td>
<td>3.1 (2.0 to 5.3)</td>
<td>3.3 (2.0 to 5.5)</td>
</tr>
<tr>
<td>Angiotensin I receptor</td>
<td>3.2 (2.0 to 5.2)</td>
<td>3.0 (2.0 to 5.0)</td>
<td>2.8 (2.0 to 4.8)</td>
</tr>
</tbody>
</table>

M235T/DD = 0.06; MT = 0.03; TT = 0.06

Values are means (SD). NS comparing groups within each gene polymorphism.

Discussion

Our 6-yr observational follow-up study of a large cohort of white patients with type 1 diabetes demonstrated that, in addition to nongenetic progression promoters, genetic factors play a role in progression of DN during established renoprotective therapy with ACE-I. The D allele of the ACE/ID polymorphism accelerates time to doubling of s-creatinine or ESRD. Furthermore, we developed a new concept suggesting that interaction between polymorphisms in the RAS influences progression of DN. The validity of this hypothesis needs future confirmation.

In the present study, patients who were treated with ACE-I were selected because this is a homogeneous, well-characterized group receiving recommended renoprotective therapy. Consequently, our results are directly applicable in a current clinical setting but cannot be extrapolated to patients who are not treated with ACE-I.

The prognosis of patients with DN has improved dramatically during the past 25 yr (1). However, the decline in GFR still varies between approximately −3 and 24 ml/min per yr in the present population. Our study showed that, in addition to the genetic factors, elevated BP, albuminuria, and hemoglobin A1c are independent risk factors for excessive loss of GFR and doubling of s-creatinine/ESRD, whereas cholesterol was associated only with the last. Because the above-mentioned nongenetic risk factors explain only approximately 30 to 50% of the variation in loss of GFR (1, 2), the search for new nongenetic and genetic risk factors continues.

Until now, the ACE/ID polymorphism has been the most extensively studied of the investigated sites of genetic variation. Originally, an increased level of circulating ACE was
Table 3. Clinical and biochemical variables according to increasing number of $M$ (angiotensinogen [M235T])/D (ACE [I/D])/A (angiotensin II receptor $A^{T66C}$) alleles in 169 patients with type 1 diabetes and diabetic nephropathy treated with ACE-I$^a$

<table>
<thead>
<tr>
<th>Variable</th>
<th>1–2 $M/D/A$ alleles ($n = 20$)</th>
<th>3–4 $M/D/A$ alleles ($n = 111$)</th>
<th>5–6 $M/D/A$ alleles ($n = 37$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in GFR (ml/min per yr)$^b$</td>
<td>3.1 (1.5 to 5.0)</td>
<td>3.0 (1.2 to 5.6)</td>
<td>4.1 (2.2 to 6.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Doubling of s-creatinine or ESRD (%)$^c$</td>
<td>15 (4 to 39)</td>
<td>27 (19 to 36)</td>
<td>43 (28 to 60)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death (%)$^c$</td>
<td>5 (0 to 27)</td>
<td>14 (8 to 22)</td>
<td>19 (9 to 36)</td>
<td>NS</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>146 (15)/81 (7)</td>
<td>137 (15)/80 (7)</td>
<td>137 (14)/82 (8)</td>
<td>0.05/0.40</td>
</tr>
<tr>
<td>Albuminuria ($\mu$g/min)$^d$</td>
<td>502 (301 to 799)</td>
<td>420 (329 to 536)</td>
<td>410 (249 to 675)</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin $A_1c$ (%)</td>
<td>9.1 (1.2)</td>
<td>9.3 (1.1)</td>
<td>9.3 (1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.3 (0.7)</td>
<td>5.6 (1.0)</td>
<td>5.7 (1.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

$^a$ Values are means (SD).

$^b$ Median (interquartile range).

$^c$ With 95% CI.

$^d$ Geometric mean with 95% CI.

Figure 2. Kaplan-Meier estimation of time to doubling of s-creatinine or ESRD according to number of $M/D/A$ alleles (left truncated from onset of nephropathy to start of follow-up). --- ---, patients with one to two $M/D/A$; ---- ----, patients with three to four $M/D/A$ alleles; --- ---, patients with five to six $M/D/A$ alleles. Vertical bars represent standard errors. Rate ratio 1.42 per allele (95% CI, 1.07 to 1.88; $P = 0.015$ in Cox proportional hazards model correcting for other risk factors [see text]).

associated with diabetes and microvascular complications (19). Studies of patients both with and without diabetes have shown that the $ACE/ID$ polymorphism influences the phenotypic variation of serum ACE (20,21). An association between the $D$ allele and the development of DN has been proposed by recent meta-analyses (22,23). Prospective and cross-sectional studies in patients with type 1 and type 2 diabetes with microalbuminuria have suggested an association between the $D$ allele and severe structural kidney changes (24,25).

In a study of progression of DN, we originally reported patients who carried the $DD$ allele to have an accelerated loss of GFR during 7 yr of ACE-I compared with patients with $ID$ and $II$ genotypes in 35 patients with type 1 diabetes and DN (3). However, in 60 spontaneously normotensive patients with type 1 diabetes and DN and very slow decline in GFR (1.2 ml/min per yr), this association was not found (26). In accordance, another study found an insignificant trend toward a deleterious effect of the $D$ allele in 86 patients with type 1 diabetes (5), but differences in antihypertensive treatment between genotypes was not accounted for. In the present study, differences in ACE-I dose or other antihypertensive treatment did not bias our findings. A small prospective study including 24 patients with type 1 diabetes and DN did not have the power to find a genetic impact on progression to ESRD (8). In type 2 diabetes, a damaging impact of the $D$ allele on loss of calculated creatinine clearance has been reported (4). In a retrospective follow-up study of 359 patients with type 2 diabetes, the authors showed a reduced renal survival time from onset of diabetes in patients with the $DD$ genotype (27). Case-control studies of the impact of the $ACE/ID$ on progression of DN have shown conflicting results (6,7,9,10,28–31) but carry the risk of selection bias, mixture of populations and phenotypes, and selective dropout.

Individual linear regression analyses have been shown to be a reliable method for estimation of rate of decline of GFR in diabetic and nondiabetic nephropathies (32–37). However, the comparison of rate of decline in GFR between genotypes in the present study is vulnerable to the well-established large interindividual variation (1). In agreement, our observed confidence intervals indicate differences in rate of decline in GFR of up to 2 ml/min per yr between genotypes within each polymorphism. This is probably the main reason underlying the apparent difference in magnitude of the impact of the $ACE/ID$ polymorphism on rate of decline in the GFR and doubling of s-creatinine/ESRD seen in our study. In addition, when rate of decline in GFR is slow, as in the present study, a time-to-event analysis has greater statistical power to detect differences than an analysis based on the slope of GFR (38). The Ramipril Efficacy in Nephropathy trial and Modification of Diet in Renal Disease (MDRD) studies support the validity of this analysis in nondiabetic nephropathies (39,40).

Experience from clinical trials of antihypertensive treatment in DN has revealed an initial faster rate of decline in GFR as compared with the long-term sustained decline in GFR (41).
However, this confounding influence on progression of DN in our study is minimal, because nearly all patients received ACE-I treatment at the time of the first GFR measurement.

The isolated role of the angiotensinogen (M235T) polymorphism on the progression of DN has been addressed in six studies (also reporting on the ACE/ID). One case-control study of 69 patients found increased frequency of the TT genotype among patients with ESRD (7), whereas four other studies failed to find an association in type 1 (6,29) and type 2 diabetes (10,30). In accordance, negative findings were also reported from a small prospective study (8).

With respect to the angiotensin II type 1 receptor (A1166→C), one study of Japanese patients with type 2 diabetes reported an impact of the C allele on progression of DN in a small number of women (27). Three case-control studies (6,29,30) did not find any association with impaired renal function in patients with diabetes.

Complete evaluation of genetic interaction between three polymorphisms would require comparisons of the 27 possible combinations of genotypes, but our study was not powered for this approach. Instead, we made a genetic interaction analysis in which variation in three polymorphisms was reduced to one variable. A key issue for this analysis is the identification of which variants were the potential “bad” alleles. The basis of our genetic model is synergistic interplay between different genetic sites, as recently described in insulin resistance (42), another disease with multifactorial cause. Therefore, we accepted the identification of potential “bad” alleles from the statistical model including the three polymorphisms as separate variables, even though two polymorphisms had no single-gene effects. This identification of the M and A alleles was supported by the insignificant single-gene trends in number of patients doubling their s-creatinine or reaching ESRD (Table 2). We found a clinical relevant impact of the total number of M, D, and A alleles on loss of GFR during ACE-I, which was confirmed in the survival analysis of time to doubling of s-creatinine or development of ESRD.

As to the underlying mechanisms of the observed genetic interaction, one suggestion is that upregulation of one genetic RAS component is compensated by downregulation of other genes, thereby causing little overall activation of the system. On the contrary, when several genes encoding different RAS components are simultaneously altered, the system is not able to compensate, resulting in a synergistic activation of RAS. In addition, it is possible that presence/absence of the investigated RAS mutations influences gene regulation and thereby changes sensitivity to feedback mechanisms based on other RAS components. Finally, linkage disequilibrium with other nearby sites may contribute.

Our interaction new model is partly supported by previous findings in nondiabetic renal disease (7,43). Importantly, ACE-I are known to stimulate gene expression of, for example, ACE (44), which may result in specific differences between genotypes during current renoprotective therapy. Studies of single-gene effects on response to RAS blockade in hypertensive patients (45) and in patients with hypertension and left ventricular hypertrophy (46) supports the identification of the M allele of the angiotensinogen (M235T) and the A allele of the angiotensin II type 1 receptor (A1166→C) polymorphisms as risk alleles. In a study primarily investigating the risk for development of diabetic nephropathy, in which half of the patients were treated with ACE-I, Marre et al. (6) demonstrated an interaction between the D and the T alleles.

Because we identified and genotyped patients after the onset of DN, selective dropout as a result of early increased mortality associated with certain genotypes is a potential bias. The D allele has been associated with cardiovascular disease in patients with type 1 diabetes and DN (47) and with increased 3-yr mortality in a small study of 56 patients with type 2 diabetes and proteinuria (4). However, genotype distributions were in Hardy-Weinberg equilibrium, and allele frequencies in our study were comparable with nondiabetic patients (48–50) and patients with type 1 diabetes with and without DN with regard to the ACE/ID polymorphism (23), suggesting minimal dropout. Furthermore, the duration of DN at time of identification was <5 yr, and all known nongenetic risk factors for loss of GFR were similar among patients with different RAS genotypes. If our material suffers from preferential dropout of patients with the D allele, then the true effect of the ACE/ID might be even more pronounced.

As this is an observational follow-up study, the type and dose of antihypertensive treatment have been adjusted throughout the study period. Even though the number of different antihypertensive drugs in addition to the median dose of ACE-I were comparable between patients with different genotypes, we cannot completely exclude such a bias.

Patients in the present study had a poor metabolic control; however, because this is an observational clinic-based study, this reflects the general situation for patients with DN (1). Improving the renal outcome of patients with diabetic nephropathy by optimizing glycemic control remains a challenge in the diabetes clinic.

In conclusion, our study of patients with type 1 diabetes suggests that in addition to nongenetic risk factors, the ACE/ID polymorphism alone and in interaction with other RAS polymorphisms play a role in progression of DN during ACE-I.

Acknowledgments

P. Carl Petersens Foundation, Copenhagen, The Danish Medical Association Research Fund, and The European Commission (contract no. QLG2-CT-2001-01669) supported the study.

We express appreciation to Birgitte V. Hansen, Tina R. Juhl, Berit R. Jensen, Ulla M. Smidt, and Inge-Lise Rossing for technical assistance.

References


---

Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/