Insulin resistance characterizes type 1 diabetes in patients with albuminuria. A PC-1 glycoprotein amino acid variant, K121Q, is associated with insulin resistance. We examined the impact of the PC-1 K121Q variant on the rate of decline of the glomerular filtration rate (GFR) by creatinine clearance derived from the Cockcroft-Gault formula in 77 type 1 diabetic patients with albuminuria who were followed for an average of 6.5 years (range 2.5–15). Patients carrying the Q allele (n = 22; 20 with KQ and 2 with QQ genotypes) had a faster GFR decline than those patients with the KK genotype (n = 55) (median 7.2 vs. 3.7 ml·min⁻¹·year⁻¹; range 0.16 to 16.6 vs. –3.8 to 16.0 ml·min⁻¹·year⁻¹; P < 0.001). Significantly more patients carrying the Q allele belonged to the highest tertile of GFR decline (odds ratio = 5.7, 95% CI 4.1–7.2, P = 0.02). Levels of blood pressure, HbA₁c, and albuminuria were comparable in the two genotype groups. Albuminuria (P = 0.001), mean blood pressure (P = 0.046), and PC-1 genotype (P = 0.036) independently correlated with GFR decline. Because all patients were receiving antihypertensive treatment, the faster GFR decline in the patients carrying the Q allele could be the result of reduced sensitivity to the renoprotective effect of antihypertensive therapy. PC-1 genotyping identifies type 1 diabetic patients with a faster progression of diabetic nephropathy. Diabetes 49:521–524, 2000

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S.D.C. and A.A. contributed equally to this work.

AER, albumin excretion rate; ANOVA, analysis of variance; DN, diabetic nephropathy; GFR, glomerular filtration rate; MAP, mean arterial pressure.
Clinical features of 77 type 1 diabetic patients with albuminuria according to PC-1 K121Q genotype

<table>
<thead>
<tr>
<th></th>
<th>KK</th>
<th>KQ + QQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.3 ± 1.2</td>
<td>41.7 ± 2.1</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>36/19</td>
<td>12/10</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>26.2 ± 1.2</td>
<td>25 ± 1.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 ± 0.4</td>
<td>24.4 ± 0.5</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.8 ± 0.2</td>
<td>5.6 ± 0.2</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.7 ± 0.2</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>8.5 ± 0.2</td>
<td>8.9 ± 0.4</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>99 ± 1.3</td>
<td>100 ± 1.7</td>
</tr>
<tr>
<td>AER (mg/day)</td>
<td>460 (50–4,800)</td>
<td>480 (90–1,300)</td>
</tr>
<tr>
<td>Duration of follow-up (years)</td>
<td>7.2 (2.5–15.0)</td>
<td>6.0 (2.5–15.0)</td>
</tr>
</tbody>
</table>

Data are means ± SE or median (range). *ACE inhibitors were used for an average of 5 ± 4 years in KK vs. 4 ± 3 years in Q-carrying patients (NS).

FIG. 1. Rate of GFR decline in 77 type 1 diabetic patients with albuminuria according to PC-1 K121Q genotype. — , Median values.

PC-1 genotype

FIG. 1. Rate of GFR decline in 77 type 1 diabetic patients with albuminuria according to PC-1 K121Q genotype.
determinants of DN progression is available. We believe, therefore, that properly conducted longitudinal retrospective studies, the present study among which is one of the largest, can still provide useful information.

In conclusion, our data show that the PC-1 Q121 amino acid variant is associated with a faster rate of DN progression in type 1 diabetic patients with albuminuria. PC-1 genotyping may help, therefore, in identifying fast progresor patients at an early stage of diabetic renal disease and target intensive therapy.

RESEARCH DESIGN AND METHODS

Patients. Type 1 diabetes was defined as 1) disease onset before 30 years of age, 2) evidence of ketosis at diagnosis, and 3) the absolute need of continued insulin therapy within 6 months of diagnosis. DN was defined as the presence of persistent proteinuria at the beginning of the follow-up and evidence of diabetic retinopathy. Persistent proteinuria was diagnosed if, on at least two consecutive occasions, the following criteria were fulfilled: AER >300 mg/24 h and/or albumin-to-creatinine ratio >30 mg/mmol on morning urine sample (n = 55) or a urine sample dipstick positive for protein (1+ or more) (n = 22).

Of 175 European patients with type 1 diabetes and DN who were seen from January 1995 to April 1997 in the diabetes units of five centers (four in Italy and one in the UK), 169 fulfilled the following selection criteria for participating in the study: age <70 years, available medical information dating back 2 or more years, and measurements of serum creatinine on five or more occasions. DNA for PC-1 genotyping was available in 77 of these 81 patients (31 from the U.K. and 46 from Italy). The average follow-up was 6.5 years (range 2.5–15). At the time of sampling for DNA, all patients underwent a standard clinical examination, which included two measurements of blood pressure to the nearest 2 mmHg in the sitting position after at least a 5-min rest using a mercury sphygmomanometer and an appropriate sized cuff. Diastolic blood pressure was recorded at the disappearance of Korotkoff sound (phase V). MAP was calculated as diastolic plus one-third of the pulse pressure. Serum creatinine was measured using the Jaffe reaction-rate method (Hitachi 717 Autoanalyzer; Hitachi, Tokyo), glycerated hemoglobin was measured by high-performance liquid chromatography (Diagnosis Analyzer; Bio-Rad, Richmond, CA), and urinary albumin concentration was measured in three timed 24-h urine collections by a nephelometric method (Behring Nephelometer Analyzer; Marburg, Germany). On average, serum creatinine measurements were available on an 8-month basis, and creatinine clearance was calculated with the Cockroft-Gault formula (18) and used as a measure of GFR. To validate the Cockroft-Gault formula as a measure of GFR, its predictive accuracy for GFR was assessed in a subset of 45 patients in whom simultaneous measurements of CR-EDTA GFR were available. GFR calculated with the Cockroft-Gault formula correlated highly significantly with that measured by CR-EDTA (r = 0.851, P = 0.001). For the GFR decline, analysis of the means of the differences of these two methods as proposed in preliminary studies (24,25), adjustment for multiple comparisons was applied.

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All subjects gave their informed consent to participate in the study, which was performed according to the Declaration of Helsinki guidelines and with the approval of the local ethical committees.

Genotyping. High molecular weight DNA for genotyping was extracted from peripheral blood (5–10 ml) that was taken into EDTA-containing tubes, was frozen as whole, and was stored at −30°C until extraction. Genomic DNA was extracted by proteinase K–phenol/chloroform standard method (17,23), resuspended in 10 mmol/l Tris-HCl, pH 8.0, and 1 mmol/l EDTA, and stored at 4°C. The polymerase chain reaction technique, specific primers, and experimental conditions used for genotyping have been previously described (17).

Statistical analysis. Data are reported as means (± SE) or median (range). Mean comparisons were made by unpaired Student’s t test or Mann-Whitney U tests, as appropriate. A P value <0.05 was considered to be significant. Because part of this series has been studied to test the association of GFR decline with other genes (19,32), disease onset before 30 years of age, and multiple variate analyses were used to correlate independent variables of progression with the dependent variable, that being the rate of GFR decline. For this analysis, AER values were logarithmically transformed.

REFERENCES

