Renal Changes on Hyperglycemia and Angiotensin-Converting Enzyme in Type 1 Diabetes

Michel Marre, Béatrice Bouhanick, Gilles Berrut, Yves Gallois, Jean-Jacques Le Jeune, Gilles Chatellier, Joël Menard, François Alhenc-Gelas

Abstract—Hyperglycemia causes capillary vasodilation and high glomerular capillary hydraulic pressure, which lead to glomerulosclerosis and hypertension in type 1 diabetic subjects. The insertion/deletion (I/D) polymorphism of the angiotensin I–converting enzyme (ACE) gene can modulate risk of nephropathy due to hyperglycemia, and the II genotype (producing low plasma ACE concentrations and probably reduced renal angiotensin II generation and kinin inactivation) may protect against diabetic nephropathy. We tested the possible interaction between ACE I/D polymorphism and uncontrolled type 1 diabetes by measuring glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) during normoglycemia (≈5 mmol/L) and hyperglycemia (≈15 mmol/L) in 9 normoalbuminuric, normotensive type 1 diabetic subjects with the II genotype and 18 matched controls with the ID or DD genotype. Baseline GFR (145±22 mL/min per 1.73 m²) and ERPF (636±69 mL/min per 1.73 m²) of II subjects declined by 8±10% and 10±9%, respectively, during hyperglycemia; whereas baseline GFR (138±16 mL/min per 1.73 m²) and ERPF (607±93 mL/min per 1.73 m²) increased by 4±7% and 6±11%, respectively, in ID and DD subjects (II versus ID or DD subjects: P=0.0007 and P=0.0005, for GFR and ERPF, respectively). The changes in renal hemodynamics of subjects carrying 1 or 2 D alleles were compatible, with a mainly preglomerular vasodilation induced by hyperglycemia, proportional to plasma ACE concentration (P=0.024); this was not observed in subjects with the II genotype. Thus, type 1 diabetic individuals with the II genotype are resistant to glomerular changes induced by hyperglycemia, providing a basis for their reduced risk of nephropathy. (Hypertension. 1999;33:775-780.)

Key Words: glomerular disease ■ diabetic nephropathy ■ genetics ■ angiotensin-converting enzyme

Hypertension in excess in individuals with type 1 diabetes is entirely accounted for by diabetic nephropathy; however, type 1 diabetics do not all run the same risk of diabetic nephropathy, regardless of their blood glucose control. Family studies suggest that this may be due to differences in their genetic backgrounds. The angiotensin I–converting enzyme (ACE) gene was tested for its association with diabetic nephropathy for several reasons. First, high intraglomerular angiotensin II (Ang II) levels cause intraglomerular hydraulic pressure to increase, which favors diabetic glomerulosclerosis, and low ACE concentrations can limit intrarenal Ang II generation. Second, an insertion/deletion (I/D) polymorphism in intron 16 of the ACE gene accounts for much of the interindividual difference in plasma ACE and therefore provides a physiological basis for a genetic susceptibility to glomerular lesions. Last, ACE inhibition prevents or retards diabetic nephropathy. We suggested a dominant effect of the ACE D allele on the risk of diabetic nephropathy and protection with the II genotype due to low plasma ACE levels. In experimental diabetes, high blood glucose causes high intraglomerular hydraulic pressure, glomerular filtration rate (GFR), and renal plasma flow, just as in type 1 diabetes. In the present study, changes in glomerular capillary pressure were therefore estimated from those in GFR, effective renal plasma flow (ERPF), and mean arterial pressure (MAP) produced by the transition from normoglycemia to hyperglycemia in type 1 diabetics selected for their genetic predisposition to low or high ACE levels. Thus, case subjects had the II genotype, and controls had the ID or DD genotype. As high urinary albumin excretion reflects changes in glomerular structure in type 1 diabetics, which can affect renal hemodynamics, all the type 1 diabetics studied had normal blood pressure and albumin excretion.

Methods

Subject Selection
Selection criteria were as follows: type 1 diabetes for 2 years or more, with onset before the age of 35 years; men or nonpregnant women; age 18 to 50 years; no obesity (body mass index <27 kg/m²); no or background diabetic retinopathy; normal clinic blood pressure (≤130/85 mm Hg) and urinary albumin excretion (<30 mg/24 h on 3 consecutive urine samples); no chronic or acute illness other than type 1 diabetes; and no medication other than exogenous insulin or
contraceptive pills for women. A group of 416 subjects (209 men and 207 women) were eligible for the study from the 696 type 1 diabetics who attended the Adult Diabetic Clinic in Angers University Hospital (France) during 1995. As a result, 179 men and 153 women gave their written informed consent for blood sampling to have their ACE I/D genotypes determined and for kidney function studies as described below. Their clinical characteristics were not different from those of individuals who refused the study. We selected the cases with II genotype consecutively (about 20% of individuals attending our clinic) and matched them with 2 controls with ID or DD genotype for gender, age (within 5 years), and diabetes duration (within 5 years). Then, 11 groups of case-control subjects participated in a kidney function study. Five studies could not be validated because of technical problems, and only 1 could be repeated. Finally, 9 triplets of cases and matched controls were studied, a number sufficient to test our hypothesis. The study protocol was approved by the Ethics Committee of Angers University Hospital.

**Kidney Function Studies**

Subjects arrived at the clinic the evening before study, with 24-hour urine collections for albumin and sodium measurements. They were given their usual dose of regular insulin subcutaneously to cover their evening meal and then were infused intravenously with insulin (Actrapid, Novo-Nordisk; diluted in physiological saline to 1 IU/mL) via a catheter inserted into a forearm vein. Another catheter was inserted into a vein of the contralateral forearm for blood sampling during the study. The insulin infusion rate was adjusted during the night as described previously so that subjects were nearly normoglycemic in the morning. Because insulin can affect kidney function, the insulin infusion rate was then continued unchanged. Blood samples were taken at 7 AM with subjects in the supine position for measurements of plasma ACE, renin and aldosterone, and glycohemoglobin. Kidney function was studied as described previously using the primed infusion of 125I-iodothalamite plus 131I-hippurate under forced water diuresis until completion of the study. There were 6 successive 30-minute periods, and blood was sampled (5 mL) in the middle of each period. The concentrations of 125I, 131I, free insulin, and glucose on each plasma sample as well as the concentrations of 125I and 131I in urine samples were measured. No exogenous glucose was infused during the first 3 periods (normoglycemic period). Exogenous glucose (0.4 g/kg body wt in the form of glucose [30 g/100 mL solution] was infused during the first 10 minutes of the fourth period for blood glucose to be raised to approximately 15 mmol/L for the last 3 periods of the study (hyperglycemic period). MAP was recorded with an automatic device as described previously. The effect of time on serial measurements of GFR and ERPF during the study was estimated in preliminary experiments performed on 9 men and 3 women, aged 27±6 years and 7 normoalbuminuric, normotensive type 1 diabetics (3 men and 4 women, aged 27±12 years), using the same protocol, except that the healthy controls were not infused with insulin or glucose and the type 1 diabetics were not given exogenous glucose.

**Determinations**

The ACE I/D polymorphism and plasma concentrations were determined as described previously. Glycohemoglobin was measured by high-performance liquid chromatography, sodium by flame photometry, glucose by the glucose-oxidase method, plasma renin by immunoradiometry, and aldosterone by radioimmunoassay. Plasma free insulin was extracted with polyethylene glycol and measured by radioimmunoassay.

GFR and ERPF were estimated from urinary clearances of 125I-iodothalamite and 131I-hippurate, respectively. The renal coefficient of extraction of 131I-hippurate was not estimated because catheterization of the renal vein was not ethically acceptable and because this maneuver is not necessary for estimating changes in renal blood flow from those of 131I-hippurate clearance. Filtration fraction (FF) was calculated as GFR/ERPF. Total renal resistance (TRR, expressed as dyne · s · cm⁻²/1.73 m²) was calculated as MAP/ERPF×(1/Ht), where Ht is hematocrit. The difference between ERPF and GFR was also calculated, because true efferent glomerular resistance is a function of the reciprocal of this difference. Variables were all measured or calculated within each of the 6 study periods. However, steady state may not have been reached during periods 1 (injection of the priming doses of tracers) and 3 (glucose infusion). Therefore, values obtained only during periods 2 and 3 were averaged and are referred to as values of the normoglycemic period, and values of periods 5 and 6 were also averaged and are referred to as values of the hyperglycemic period.

**Statistical Analysis**

Data are given as mean±SD or medians (ranges). A repeated-measures ANOVA was used to test the effects of group (crossed factor: II versus non-II; II versus ID versus DD), of time (repeated factor: normoglycemia versus hyperglycemia), and of their interaction on the studied variables. Intergroup comparisons and correlations were performed using the Mann-Whitney U, Kruskal-Wallis, and Spearman’s rank tests. The primary purpose of this study was to evaluate the effect of changes in GFR caused by hyperglycemia in type 1 diabetics with the II genotype and in controls. Because we had no preliminary data, we used a sequential design: Taking an overall two-sided level of significance of 5%, we used a nominal significance level of 0.01 for the ninth stage of comparison and stopped the study then. Analysis of a genotype effect (II, ID, and DD) was performed in a secondary analysis.

**Results**

**Effect of Type 1 Diabetes and Time on Serial Measurements of GFR and ERPF**

Initially, GFR was higher in type 1 diabetics than in control subjects (152±35 versus 112±16 mL/min per 1.73 m²); it declined with time in both groups down to 146±34 and 109±12 mL/min per 1.73 m², respectively, but the intergroup difference was not affected by time (ANOVA: group effect, P=0.0274; time effect, P=0.0096; group-time interaction, P=0.0812). Initial ERPF did not differ in type 1 diabetics and control subjects (696±137 versus 733±208 mL/min per 1.73 m²); it declined with time equally in both groups (570±122 and 559±98 mL/min per 1.73 m², respectively; ANOVA: group effect, P=0.9142; time effect, P=0.0002; group-time interaction, P=0.9275).

**Subject Characteristics According to ACE I/D Genotype**

Subject characteristics did not differ according to ACE genotype (Table 1). Plasma ACE was lower in subjects with the II genotype than in the other subjects. Plasma renin and aldosterone values and urinary sodium did not differ.

**Experimental Conditions During Kidney Function Tests**

Plasma glucose rose from 5.7±1.7 mmol/L during the normoglycemic period to 14.6±2.2 mmol/L during the hyperglycemic period, and plasma free insulin declined slightly with time from 13±7 to 12±6 mIU/mL, without any difference between groups. Urine volume was 12±4 mL/min throughout the study, was not affected by time, and did not differ between groups.

**Effect of Hyperglycemia on Kidney Function in Type 1 Diabetics According to ACE I/D Genotype**

Baseline values of the studied variables were not statistically different according to genotype (Table 2). In subjects with the
II genotype, GFR declined from the normoglycemic to the hyperglycemic period, and it increased in subjects without the II genotype. ACE I/D polymorphism had an effect on changes in GFR, but there was no difference between subjects with the ID or DD genotype. In subjects with the II genotype, ERPF declined from the normoglycemic to the hyperglycemic period, and it increased in subjects without the II genotype. Changes in ERPF were dependent on ACE I/D polymorphism, and there was a nonsignificant difference between subjects with the ID versus those with the DD genotype. Baseline MAP values and changes from normoglycemia to hyperglycemia did not differ according to genotype. TRR did not differ according to the ACE I/D genotype during normoglycemia; however, TRR values were more reduced by hyperglycemia in subjects without the II genotype than in those with it, and there was no difference between subjects having the ID or DD genotype. The difference between ERPF and GFR was accentuated by hyperglycemia in subjects without the II genotype compared with those with it, but there was no significant difference between subjects having the ID or DD genotype. Baseline FF values did not differ from one genotype to another, nor did the changes in them produced by hyperglycemia.

**Relationship Between Plasma ACE Levels and Changes in Kidney Function Induced by Hyperglycemia**

The Figure shows the relationship between plasma ACE levels and changes in kidney function induced by hyperglycemia. Percentage changes in GFR induced by hyperglycemia were not related to plasma ACE concentration, but percentage changes in ERPF were linked to plasma ACE, as were the decline in TRR and the rise in the difference between ERPF and GFR.

**Discussion**

In this study, the renal hemodynamic responses to hyperglycemia of normotensive, normoalbuminuric type 1 diabetics differed clearly between subjects with the II genotype and those with other genotypes. Subjects carrying at least 1 D allele underwent renal vasodilation and a rise in GFR in response to hyperglycemia related to plasma ACE, whereas those with the II genotype displayed no such response. These results support the hypothesis that the ACE I/D polymorphism can affect renal hemodynamics through its association with plasma ACE. The hemodynamic changes that occurred in the type 1 diabetics with the ACE D allele during hyperglycemia were similar to those observed by Hostetter et al at the single nephron level in moderately hyperglycemic rats, ie, a rise in mean glomerular capillary hydraulic pressure. Conversely, the lack of a renal hemodynamic response to hyperglycemia seen in the type 1 diabetics with the II genotype (or with low plasma ACE levels) was similar to the findings of Zatz et al during pharmacological ACE inhibition, where the glomerular hydraulic pressure was low. Thus, our findings support the concept that type 1 diabetics with the II genotype and low plasma ACE levels do not develop high glomerular capillary hydraulic pressure (which causes glomerulosclerosis) in response to hyperglycemia, and they provide a physiological basis for the apparent renal protection in type 1 diabetics with the II genotype reported previously.

We found small time-dependent declines in GFR and ERPF during the morning in our preliminary experiments, as described previously. We therefore took this effect of time into account in the analysis of renal hemodynamic changes. These changes can be linked solely to changes in blood glucose, as plasma insulin levels did not vary during the same time.

The rise in ERPF in type 1 diabetics carrying the D allele during hyperglycemia is similar to that previously reported in unselected type 1 diabetics and in experimental diabetest and is consistent with a global capillary vasodilation due to hyperglycemia, a phenomenon that can affect preglomerular arterioles. Thus, afferent renal resistance was cer-

---

**TABLE 1. Characteristics of IDDM Subjects**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>II (n=9)</th>
<th>Non II (n=18)</th>
<th>ID (n=8)</th>
<th>DD (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34±11</td>
<td>34±10</td>
<td>34±12</td>
<td>34±9</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>6/3</td>
<td>12/6</td>
<td>5/3</td>
<td>7/3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.5±2.1</td>
<td>22.7±2.5</td>
<td>22.2±2.7</td>
<td>23.2±2.3</td>
</tr>
<tr>
<td>IDDM duration, y</td>
<td>15±11</td>
<td>14±9</td>
<td>16±8</td>
<td>12±9</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>8.7±1.2</td>
<td>8.9±1.2</td>
<td>8.5±1.4</td>
<td>9.2±2.0</td>
</tr>
<tr>
<td>Diabetic retinopathy, no/background</td>
<td>6/3</td>
<td>13/5</td>
<td>5/3</td>
<td>8/2</td>
</tr>
<tr>
<td>Systolic/diastolic BP, mm Hg</td>
<td>121±9/73±7</td>
<td>118±10/73±7</td>
<td>118±7/71±6</td>
<td>118±13/74±7</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>146±57</td>
<td>155±72</td>
<td>158±74</td>
<td>153±74</td>
</tr>
<tr>
<td>Urinary albumin, mg/24 h</td>
<td>3 (2–10)</td>
<td>4 (2–22)</td>
<td>4 (2–22)</td>
<td>6 (2–16)</td>
</tr>
<tr>
<td>Plasma renin, ng/L</td>
<td>10±6</td>
<td>13±5</td>
<td>11±5</td>
<td>15±5</td>
</tr>
<tr>
<td>Plasma aldosterone, pmol/L</td>
<td>470±278</td>
<td>393±231</td>
<td>385±189</td>
<td>400±269</td>
</tr>
</tbody>
</table>

*Results are mean±SD or medians (range). I indicates insertion; D, deletion; IDDM, insulin-dependent diabetes mellitus; and BP, blood pressure.*

*II vs non II, P=0.0136 (Mann-Whitney U test); †effect of genotype (II/ID/DD), P=0.0362 (Kruskall-Wallis test); ‡ID vs DD, P=0.4772 (Mann-Whitney U test).*
Table 2. Effect of Hyperglycemia on GFR, ERPF, TRR, ERPF—GFR, and FF in IDDM Subjects According to ACE I/D Genotype

<table>
<thead>
<tr>
<th>Parameter</th>
<th>II (n = 9)</th>
<th>Non II (n = 18)</th>
<th>P, II vs Non II</th>
<th>ID (n = 8)</th>
<th>DD (n = 10)</th>
<th>P, Genotype Effect</th>
<th>P, ID vs DD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GFR, mL/min per 1.73 m²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>145 ± 22</td>
<td>138 ± 16</td>
<td>0.7892*</td>
<td>140 ± 17</td>
<td>137 ± 16</td>
<td>0.9148*</td>
<td>0.7287*</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>133 ± 22</td>
<td>144 ± 19</td>
<td>0.9365†</td>
<td>145 ± 17</td>
<td>143 ± 21</td>
<td>0.9377†</td>
<td>0.0197†</td>
</tr>
<tr>
<td>ΔGFR</td>
<td>−12 ± 16</td>
<td>+6 ± 9</td>
<td>0.001‡</td>
<td>+5 ± 8</td>
<td>+7 ± 11</td>
<td>0.0047‡</td>
<td>0.7492‡</td>
</tr>
<tr>
<td>% Change</td>
<td>−8.1 ± 10</td>
<td>+4.3 ± 6.7</td>
<td>0.0007§</td>
<td>+3.8 ± 6.4</td>
<td>+4.6 ± 7.3</td>
<td>0.003∥</td>
<td>0.6567§</td>
</tr>
<tr>
<td><strong>ERPF, mL/min per 1.73 m²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>639 ± 69</td>
<td>607 ± 93</td>
<td>0.5328*</td>
<td>636 ± 117</td>
<td>584 ± 66</td>
<td>0.6979*</td>
<td>0.6081*</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>538 ± 75</td>
<td>645 ± 119</td>
<td>0.6532†</td>
<td>644 ± 129</td>
<td>645 ± 117</td>
<td>0.8471†</td>
<td>0.0265†</td>
</tr>
<tr>
<td>ΔERPF</td>
<td>−68 ± 60</td>
<td>+38 ± 69</td>
<td>0.0006‡</td>
<td>+8 ± 55</td>
<td>+62 ± 73</td>
<td>0.0007‡</td>
<td>0.1028‡</td>
</tr>
<tr>
<td>% Change</td>
<td>−10.5 ± 8.7</td>
<td>+6.2 ± 11.2</td>
<td>0.0005§</td>
<td>+1.3 ± 9.2</td>
<td>+10.2 ± 11.5</td>
<td>0.0008∥</td>
<td>0.0914§</td>
</tr>
<tr>
<td><strong>TRR, dyne · s · cm⁻³ per 1.73 m²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>5335 ± 807</td>
<td>5719 ± 1129</td>
<td>0.7991*</td>
<td>5392 ± 1219</td>
<td>5981 ± 1040</td>
<td>0.7373*</td>
<td>0.5041*</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5986 ± 1114</td>
<td>5376 ± 1288</td>
<td>0.9395†</td>
<td>5277 ± 1306</td>
<td>5455 ± 1338</td>
<td>0.9354†</td>
<td>0.0422†</td>
</tr>
<tr>
<td>ΔTRR</td>
<td>+651 ± 884</td>
<td>−343 ± 673</td>
<td>0.0032‡</td>
<td>−114 ± 674</td>
<td>−526 ± 648</td>
<td>0.0073‡</td>
<td>0.2066‡</td>
</tr>
<tr>
<td>% Change</td>
<td>+12.7 ± 17.1</td>
<td>−6.1 ± 12.1</td>
<td>0.0136§</td>
<td>−1.9 ± 12.8</td>
<td>−9.4 ± 11.1</td>
<td>0.026∥</td>
<td>0.2135§</td>
</tr>
<tr>
<td><strong>ERPF—GFR, mL/min per 1.73 m²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>491 ± 63</td>
<td>469 ± 84</td>
<td>0.5171*</td>
<td>496 ± 108</td>
<td>447 ± 57</td>
<td>0.6857*</td>
<td>0.6068*</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>435 ± 61</td>
<td>501 ± 104</td>
<td>0.8262†</td>
<td>499 ± 116</td>
<td>502 ± 100</td>
<td>0.8173†</td>
<td>0.0403†</td>
</tr>
<tr>
<td>ΔERPF—GFR</td>
<td>−56 ± 50</td>
<td>+32 ± 65</td>
<td>0.0015‡</td>
<td>+3 ± 56</td>
<td>+55 ± 64</td>
<td>0.0013‡</td>
<td>0.0875‡</td>
</tr>
<tr>
<td>% Change</td>
<td>−11.9 ± 9</td>
<td>+7.1 ± 13.6</td>
<td>0.0008§</td>
<td>+1 ± 13</td>
<td>+11.9 ± 13.1</td>
<td>0.0011∥</td>
<td>0.0914§</td>
</tr>
<tr>
<td><strong>FF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>0.230 ± 0.030</td>
<td>0.231 ± 0.031</td>
<td>0.7946*</td>
<td>0.226 ± 0.039</td>
<td>0.236 ± 0.023</td>
<td>0.9575*</td>
<td>0.8889*</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0.235 ± 0.027</td>
<td>0.227 ± 0.028</td>
<td>0.7847†</td>
<td>0.230 ± 0.033</td>
<td>0.225 ± 0.025</td>
<td>0.7944†</td>
<td>0.444†</td>
</tr>
<tr>
<td>ΔFF</td>
<td>+0.005 ± 0.018</td>
<td>−0.004 ± 0.023</td>
<td>0.3168†</td>
<td>+0.004 ± 0.03</td>
<td>−0.011 ± 0.012</td>
<td>0.2031‡</td>
<td>0.1728‡</td>
</tr>
<tr>
<td>% Change</td>
<td>+2.7 ± 8.4</td>
<td>−1.2 ± 10.0</td>
<td>0.1108§</td>
<td>+2.8 ± 13.2</td>
<td>−4.5 ± 5.2</td>
<td>0.0856∥</td>
<td>0.1309§</td>
</tr>
</tbody>
</table>

Results are mean ± SD.
Abbreviations as in Table 1 and the text.
Repeated-measures ANOVA on the studied variables: *group effect; †time effect; ‡group-time interaction; §Mann-Whitney U test; ‖Kruskall-Wallis test.

In humans, as in rats, true efferent resistance is a function of the prevailing glomerular capillary hydraulic and peritubular pressures divided by the difference between renal blood flow and GFR.25 ERPF—GFR was accentuated by hyperglycemia in subjects with the D allele, in contrast to changes in subjects with the II genotype; and changes in ERPF—GFR were in proportion to plasma ACE levels. If glomerular capillary hydraulic and peritubular pressures had remained constant in our studies, then the true efferent renal resistance must have been reduced. Alternatively, glomerular hydraulic and peritubular pressures must have increased more in subjects with the D allele than in those with the II genotype if the true efferent renal resistance remained constant. Neither of these alternatives can be ruled out (and they are not mutually exclusive), because direct measurements of intraglomerular pressure are not feasible in humans. Previous studies on rats made diabetic with streptozotocin indicate that changes in renal flux comparable to those we observed are accompanied by changes in glomerular capillary hydraulic pressure.7,11 Thus, differences in changes of renal flux between individuals carrying the D allele and those with the II genotype probably indicate different changes in glomerular capillary hydraulic pressure.

The pronounced differences between ERPF and GFR produced by hyperglycemia probably also indicate a preferential glomerular vasodilation in individuals carrying the D allele. Such changes suggest an impaired pressure disequilibrium within the glomerular circulation.7 As plasma ACE concentrations can be rate-limiting for Ang II generation,8,9 the present data support the concept that the pressure disequilibrium produced by hyperglycemia within glomeruli depends on plasma ACE through Ang II generation, and perhaps also kinin degradation.

The mechanisms by which hyperglycemia produces preglomerular vasodilation have not been investigated. There may be several determinants, such as an inappropriate rise in plasma glucagon and growth hormone in response to glucose during relative insulinopenia,32,33 or changes in atrial natriuretic factor14 or prostaglandins. Glucose can also be metabolized by the tubular cells and consequently affect GFR regulation.35 Interestingly, nitric oxide release may account for the renal vasodilation that occurs in uncontrolled diabetes, as supported recently by experimental studies.30 and high glucose can cause nitric oxide release from endothelial cells.31,36 Microperfusion studies of afferent and efferent
arterioles in vitro suggest that Ang II can interact with the action of nitric oxide on preglomerular vasodilation in a dose-response fashion, whereas the efferent arteriole seems to be sensitive to Ang II only.37 These experimental results are consistent with the present data because there was a close association between the changes in ERPF and (ERPF−GFR) in response to hyperglycemia, as well as plasma ACE concentrations. Thus, constitutive Ang II levels (depending on plasma ACE8,9) will potentiate the afferent arteriolar vasodilator response to glucose, while maintaining efferent arteriolar tone.

In addition, subjects with the II genotype could display a relative renal vasodilation at baseline that would have blunted the vasodilator effect of hyperglycemia. Indeed, Fukumoto et al38 reported low renal arcuate arterial resistances in type 1 diabetics with the II versus the DD genotype. Miller et al39 also reported that young, recent type 1 diabetics with the II genotype displayed higher GFR and ERPF than others during normoglycemia. A similar trend was observed in the present study during the normoglycemic period. The fact that type I diabetics with low ACE concentrations had a relative renal vasodilation at baseline that would have blunted the vasodilator effect of hyperglycemia. This variable has shown no predictive value for subsequent diabetic nephropathy.41

Acknowledgments

This study was supported by grants from the Juvenile Diabetes Foundation International (Grant 94/325), Novo Nordisk grant CNAM-INSERM (Grant 4 AIC18), INSERM Equipe de Recherche Clinique Associee (Grant 97/BDC2/404), the Programme Hospitalier de Recherche Clinique 1996, and the Association Diabete Risque Vasculaire. The authors thank the type 1 diabetics who volunteered for this study; Franck Pean, Vincent Benoit, Gwenaelle Renoult, Gaelle Jouet-Pastre, and Patrick Gillabert for technical assistance; the nursing staff of Medecine B; and Line Godiveau, Isabelle Gouleau, and Laëtitia Martin for excellent secretarial assistance (all at the Center Hospitalier Universitaire, Angers, France). The English text was edited by Dr Owen Parkes.

References

ACE and Glomerular Hemodynamics in Diabetes


Renal Changes on Hyperglycemia and Angiotensin-Converting Enzyme in Type 1 Diabetes
Michel Marre, Béatrice Bouhanick, Gilles Berrut, Yves Gallois, Jean-Jacques Le Jeune, Gilles Chatellier, Joël Menard and François Alhenc-Gelas

*Hypertension*. 1999;33:775-780
doi: 10.1161/01.HYP.33.3.775

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/33/3/775

**Permissions**: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints**: Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions**: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org//subscriptions/