Plasma Renin Activity and Albumin Excretion 

in Teenage Type I Diabetic Subjects

A Prospective Study

Elsa P. Paulsen, Richard L. Seip, Carlos R. Ayers, Barbara Y. Croft, and Donald L. Kaiser

Plasma renin activity (PRA) may be high among teenage and young adult insulin-dependent diabetic subjects. Supine PRA and stimulated PRA were therefore measured in 50 female and 50 male diabetic subjects, 13–20 years old, diagnosed before the age of 16. Fifty percent have been restudied after 4.6±0.2 (mean±SEM) years. Initially, 43% had high PRA (supine 4.0±0.37, stimulated 12.02±0.8 ng/ml/hr angiotensin I), 45% had normal activity (supine 2.89±0.26, stimulated 6.47±0.34 ng/ml/hr/angiotensin I), and 12% had low activity (supine 1.57±0.05, stimulated 3.09±0.08 ng/ml/hr/angiotensin I). Levels were directly associated with prepubertal duration of diabetes and were inversely associated with duration of diabetes after onset of puberty but not with total duration or patient age. Within 4.6±0.2 years the percentage of subjects with high PRA fell to 13%, and the percentage of those with low PRA rose to 35%. Initially 51% of the cohort had normal albumin excretion rates (AER) at rest and during exercise equal to or less than 10 μg/min/m²; 32% had elevated rates only during exercise of 39±5 μg/min/m²; 13% had elevated rates at rest of 41±8 μg/min/m² and during exercise of 116±21 μg/min/m²; and 4% had clinical proteinuria at rest and during each exercise period equal to or greater than 150 μg/min/m². After 5 years, 58% continued to have normal AER, or their AER improved. Among these subjects PRA fell significantly. Thirty-four percent continued to have elevated AER or their AER continued to rise. PRA among these subjects remained significantly elevated. Among the 8% with clinical proteinuria, low PRA predominated. This cohort was singularly characterized by a long prepubertal duration of diabetes. Elevated angiotensin II associated with high PRA could increase glomerular capillary pressure and contribute to urinary protein loss and glomerular damage. Rapid decline to low PRA after the onset of puberty would reduce the risk of diabetic nephropathy, whereas a slow decline would enhance it. (Hypertension 1989;13:781–788)

Elevated albumin excretion rates (AER) at rest or during exercise are reported as evidence of early nephropathy.1,2 The time course for progression to clinical nephropathy, indicated by persistent proteinuria, is highly variable. In subjects who develop insulin-dependent diabetes before the age of 16, nephropathy is extremely rare before 16 years of age and does not occur before 10–15 years after onset of disease; the cumulative risk for diabetic nephropathy is between 33 and 40%.3–4

Current evidence points to increased intrarenal pressure as underlying the initiation and progression of diabetic nephropathy.5 However, factors that cause these hemodynamic changes are incompletely defined.6

Reports of high plasma renin activity (PRA) among teenage7 and young adult8 insulin-dependent diabetic subjects (IDDS) suggested that associated increases in angiotensin II (Ang II) could initiate or enhance glomerular capillary pressure and proteinuria. To explore the relation between renin activity and diabetic nephropathy, resting PRA and stimulated PRA were measured in pubertal and postpubertal IDDS in whom diabetic nephropathy would be absent or in an early form. PRA was measured prospectively for 4.6±0.2 years. Concurrent assessment of renal and neurological function was performed in each patient.

Subjects and Methods

Subjects

Fifty female and 50 male white nonobese subjects, evenly represented between 13 and 20 years of age, were randomly selected from the Adolescent

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Diabetic Clinic at the University of Virginia Medical Center and admitted to the Clinical Research Center for study. Dietary intake consisted of 50% carbohydrate, 15% protein, and 35% fat (polyunsaturated: saturated, 1.5:1.0) with restriction of refined sugar and salt according to individual taste. All had experienced the onset of diabetes before their 16th birthday and were undergoing or had completed normal puberty. The onset of puberty was taken as 11 years of age in females and 12 in males.

Fifty subjects, randomly and proportionately selected from each of four groups defined on the basis of albumin excretion rates, were restudied after 4.6±0.2 years.

Twenty-four healthy females and 24 healthy males, evenly distributed between 13 and 20 years of age and of normal height and weight without known family histories of diabetes or hypertension, underwent graded exercise tests; 10 of the 24 females and 10 of the 24 males spanning 13-20 years of age underwent measurement of supine and stimulated PRA.

All subjects and parents of those under age 18 were informed of the nature and purpose of the tests before giving consent to participate. Tests were approved by the Human Investigation Committee of the University of Virginia Medical Center.

Maximal Cycle Work Capacity

Each subject performed a continuous, graded exercise test to volitional exhaustion before each series of exercise tests.9 The highest work load sustained for 1 minute was taken as the maximal work capacity.

Submaximal Graded Exercise

Subjects performed two exercise tests on separate mornings during each admission. Tests were performed 2 hours after a light breakfast that contained no caffeinated foods or beverages and were initiated and ended with a 1-hour rest period. Daily insulin dosages were adjusted to achieve prebreakfast glucose of 200–220 mg/dl to prevent hypoglycemia during exercise.

Subjects underwent 15-minute exercise periods at 35, 60, and 85% of maximal work capacity. In the latter period the work load was alternated between 85 and 35% capacity to ensure completion of the cycling time. Blood pressure was recorded every 15 minutes during rest and every 5 minutes during exercise. Diastolic pressure was taken as the fifth Korotkoff sound during slow deflation of the cuff.

Blood pressure responses were evaluated on the basis of body size (m² body surface) and sex. Measurements of volume, albumin, β₂ microglobulin, creatinine, sodium, and potassium were made on accurately timed urine specimens collected for each period. Albumin and β₂ microglobulin were determined by radioimmunoassay using kits from Diagnostic Products Corporation (Los Angeles, California) and Phadebas, Pharmacia (Piscataway, New Jersey), respectively.

PRA, determined by the method of Sealey and Laragh,10 was measured from a sample obtained after overnight supine rest and from a sample obtained after arising and walking quietly for 3 hours. Urinary sodium excretion was measured during a 24-hour period spanning the time PRA was determined. PRA was defined as high, normal, or low on the basis of 24-hour urine sodium excretion (Figure 1).

Glomerular filtration rates (GFR), using [⁹⁹ᵐ⁹Tc] diethylenetriamine pentaacetic acid,¹¹ and effective renal plasma flow (ERPF),¹² using [¹³¹I]hippuran, were measured simultaneously by plasma disappearance of the radionuclides with the patient in the supine position. Filtration fraction (FF) was derived by dividing GFR by ERPF. Renal blood flow was calculated by dividing ERPF by 1 minus hematocrit. Renal vascular resistance (RVR) was calculated as
mean arterial blood pressure (MAP) at clearance divided by renal blood flow ($10^3$ dynes-sec-cm$/^-5$/ 1.73 m$^3$). Hemoglobin A$_1$ (Hb A$_1$) was measured by cation exchange, using a kit furnished by BioRad, Incorporated (Richmond, California).

Sympathetic nerve function was evaluated by sympathetic skin response (SSR) as part of a detailed neurological assessment of motor, sensory, and autonomic function in IDDS.

Statistical analyses were performed using Student's $t$ statistic, Duncan's multiple range test, simultaneous multivariate analysis, and the $\chi^2$ statistic or Fisher's exact test for small groups. All values are mean±SEM unless otherwise designated.

### Results

AER during graded exercise tests in the control subjects were independent of age, body surface area, and sex. Data were, therefore, combined without distinguishing for these factors. The upper limits of normal AER during the exercise test (mean±2 SD) were: initial and final rest periods, 8 and 6 $\mu$g/min/m$^2$; moderate and strenuous exercise, 2.5±0.3. Multivariate analysis of PRA in the cohort (with subjects measured once each but at varying points in the duration of the diabetes) revealed that PRA was directly associated with the subjects' prepubertal duration of diabetes ($p=0.0292$, $r=0.234$) and inversely associated with the pubertal/postpubertal duration of diabetes ($p=0.0075$, $r=0.261$). These were the strongest associations with PRA, and, once taken into account, there was no association with total duration of diabetes or patient age. Among the subjects with normal AER, those with high PRA were the youngest (15±0.4 years, $n=20$), had the shortest pubertal duration of diabetes (2.9±0.2 years), but had prepubertal durations covering a wide range (0-9 years); those with normal AER and low PRA were the oldest (19.5±0.8 years, $n=4$) and had the longest postpubertal duration of diabetes (6.7±0.5 years) (c.f., chronological ages $p<0.01$; postpubertal duration, $p<0.001$). These latter four subjects were the same age and had the same postpubertal duration of diabetes as the four with clinical proteinuria (18.8±0.5 and 6.9±0.2 years, respectively). However, they had a much shorter prepubertal duration than those with proteinuria (0.5±0.15 vs. 5.8±0.5 years, $p<0.01$). Two subjects with clinical proteinuria had high and two had normal PRA.

GFR and ERPF were greatly elevated in groups 1 and 2 (Table 2). In group 3 the GFR remained elevated, but ERPF fell. FFs were high in groups 1-3. All parameters of renal function were decreased in group 4. In groups 3 and 4, MAP and RVR were elevated above the normal levels seen in groups 1 and 2. Serum creatinine in group 3, though within the normal range, was significantly higher than values in groups 1 and 2 ($p<0.001$ and $p<0.05$, respectively). The degree of glycemic control reflected in Hb A$_1$ levels was similar among the four groups.

Significant associations were noted: AER in groups 1-3 with RVR ($p<0.02$) and with Hb A$_1$ (during exercise only, $p<0.001$), not with GFR or ERPF; RVR with FF ($p<0.001$) and PRA ($p<0.02$), not with Hb A$_1$ or GFR; Hb A$_1$ with GFR (groups 1-3, $p<0.01$, $p<0.05$, and $p<0.001$; group 4, NS), not in groups 1-3.  

### Table 1. Clinical Characteristics of 100 Subjects Based on Albumin Excretion Rates at Time of Initial Study

<table>
<thead>
<tr>
<th>AER (group)</th>
<th>Female/male</th>
<th>Percent of total (%)</th>
<th>Age (yr)</th>
<th>Duration of diabetes (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.7</td>
<td>51</td>
<td>16±2*†</td>
<td>72±4†</td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
<td>32</td>
<td>17±2</td>
<td>7±4†</td>
</tr>
<tr>
<td>3</td>
<td>1.6</td>
<td>13</td>
<td>18±2</td>
<td>11±5</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>4</td>
<td>19±3</td>
<td>14±3</td>
</tr>
</tbody>
</table>

Values of age and duration of diabetes are given as mean±SD. AER, albumin excretion rates.

* $p<0.05$, significantly different from group 2.
† $p<0.01$, significantly different from groups 3 and 4.
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**FEMALES**

<table>
<thead>
<tr>
<th>1</th>
<th>147±21*</th>
<th>622±101*</th>
<th>0.25±0.04*</th>
<th>79±6</th>
<th>84±6</th>
<th>7.7±1.2</th>
<th>0.83±0.1</th>
<th>13.4±3.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>149±27*</td>
<td>630±124†</td>
<td>0.24±0.05*</td>
<td>80±7</td>
<td>84±5</td>
<td>7.6±1.1</td>
<td>0.88±0.1</td>
<td>12.2±2.5</td>
</tr>
<tr>
<td>3</td>
<td>139±12*</td>
<td>523±91</td>
<td>0.27±0.05*</td>
<td>86±1*</td>
<td>91±4†</td>
<td>10.0±1.5†</td>
<td>0.94±0.05</td>
<td>11.4±1.6</td>
</tr>
<tr>
<td>4</td>
<td>71±30§</td>
<td>375±53*</td>
<td>0.19±0.08</td>
<td>104±17‡</td>
<td>110±17‡</td>
<td>16.5±2.5*</td>
<td>1.54±0.34†</td>
<td>13.2±1.2</td>
</tr>
</tbody>
</table>

**MALES**

| 1 | 104±30* | 553±91 | 0.18±0.01 | 79±1 | 84±3 | 8.6±1.0 | 1.0±0.015 | 6.9±0.08 |

**TABLE 2.** Parameters of Renal Function, Mean Arterial Pressure, and Hemoglobin A1 Based on Albumin Excretion Rates During Initial Study

AER (group) GFR (m/min/1.73 m²) ERPF (m/min/1.73 m²) FF MAP (mm Hg) RVR (dynes-sec-cm⁻²/m²) Cr₇ (mg/dl) Hb A₁ (%)

| 1 | 147±21* | 622±101* | 0.25±0.04* | 79±6 | 84±6 | 7.7±1.2 | 0.83±0.1 | 13.4±3.2 |
| 2 | 149±27* | 630±124† | 0.24±0.05* | 80±7 | 84±5 | 7.6±1.1 | 0.88±0.1 | 12.2±2.5 |
| 3 | 139±12* | 523±91 | 0.27±0.05* | 86±1* | 91±4† | 10.0±1.5† | 0.94±0.05 | 11.4±1.6 |
| 4 | 71±30§ | 375±53* | 0.19±0.08 | 104±17‡ | 110±17‡ | 16.5±2.5* | 1.54±0.34† | 13.2±1.2 |

Normal 111±13 553±91 0.18±0.01 79±1 84±3 8.6±1.0 1.0±0.015 6.9±0.08

Values are mean±SD. AER, albumin excretion rates; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction (GFR/ERPF); MAP, mean arterial pressure; RVR, renal vascular resistance (MAP/renal blood flow); Cr₇, serum creatinine; Hb A₁, hemoglobin A₁. For groups A, B, and C, n=30; for group D, n=65.

* p<0.0001 vs. normal values; † p<0.01 vs. normal values; ‡ p<0.001 vs. normal values; § p<0.02 vs. normal values; †† p<0.05 vs. normal values.
with ERPF, FF, or MAP; ERPF with GFR (p<0.01) and MAP (p<0.02). PRA was significantly associated with no parameter other than RVR.

The incidence of mildly abnormal sympathetic skin response was similar among subjects of each renin group: high PRA 38%, normal PRA 33%, and low PRA 40% (p=0.373).

Exercise tests performed among 50 IDDS after 4.6±0.2 years revealed that AER improved as well as worsened. Of 26 patients originally in group 1 (normal rates), 62% remained in the group, 27% moved to group 2, 8% moved to group 3, and 3% moved to group 4. Of 15 patients originally in group 2 (elevated rates during exercise only), 40% remained in the group, 60% moved to group 1, and none moved to groups 3 or 4. Of 7 patients originally in group 3 (elevated rates at rest and during exercise), 29% remained in the group, 43% moved to group 1, 14% moved to group 2, and 14% moved to group 4. Two patients in group 4 remained in the group. Overall changes from the initial study to the follow-up study were: group 1, from 51% to 56%; group 2, from 32% to 28%; group 3, from 13% to 18%; and group 4, from 4% to 8%.

Fifty-eight percent of the cohort continued to have normal AER or improved their rates. Among these subjects, PRA fell significantly (Figures 3 and 4). Thirty-four percent continued to have elevated AER, or their AER rose. PRA among these subjects remained significantly elevated (Figure 3). Among the 8% with clinical proteinuria, 25% continued to have high PRA, and 75% had achieved low PRA. Prepubertal duration of diabetes in IDDS with clinical proteinuria was significantly longer than that of the remainder of the cohort (5.3±0.8 vs. 2.5±0.5 years, p<0.05).

The distribution of high, normal, and low PRA among the IDDS shifted significantly over the 5-year period toward lower levels (Table 3.) Analysis of data reported by Christlieb et al16 among older IDDS is included in Table 3 and reveals an absence of subjects with high PRA. In this adult cohort, normal PRA predominated among subjects without nephropathy, whereas low PRA predominated among those with nephropathy.

**Discussion**

The diabetic subjects under study were grouped according to AER during graded exercise on the basis of data revealing abnormalities at rest and during exercise as evidence of early diabetic nephropathy.1,2 The results are consistent with findings in this age group.3,17,18 Prepubertal children have normal AER with abnormalities appearing during pubertal development; 16 years is the youngest age at which diabetic nephropathy was noted in a cohort of 108 youth-onset IDDS. In the present study a progression was clearly evident: elevated AER first appeared among 14-year-old subjects during exercise and progressed among 15-year-old subjects to elevated rates at rest and was accompanied by small but significant increases in resting arterial and intrarenal pressure and serum creatinine; finally, clinical proteinuria was noted in a 17-year-old subject.

PRA was measured in subjects at differing stages of their diabetes, providing longitudinal assessment for the cohort since it was not possible to follow renin activity in individual subjects from onset of
between infancy and 4 years of age and reaches adult levels by 9–10 years of age. These levels continue until a final decline occurs in the forties.

High levels of supine and stimulated PRA have been recently reported in seven IDDS, 12.5–19 years of age, in association with elevated Hb A1c, compared with normal levels in seven age-matched IDDS with normal Hb A1c and in seven age-matched healthy subjects. In the present study PRA was not significantly associated with Hb A1c.

### Table 3. Changes in Plasma Renin Activity in Diabetic Subjects Over 4.6±1.7 Years

<table>
<thead>
<tr>
<th>Diabetic nephropathy</th>
<th>IDDS</th>
<th>n</th>
<th>Age (yr)</th>
<th>Onset of diabetes (yr)</th>
<th>Duration of diabetes (yr)</th>
<th>Plasma Renin Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>I</td>
<td>48</td>
<td>16±2</td>
<td>7±4</td>
<td>56*</td>
<td>High (%)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>46</td>
<td>21±3</td>
<td>10±4.4</td>
<td>13*</td>
<td>Normal (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low (%)</td>
</tr>
<tr>
<td></td>
<td>Christlieb</td>
<td>19</td>
<td>47±4</td>
<td>25±2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>I</td>
<td>2</td>
<td>18±1</td>
<td>12±3</td>
<td>50</td>
<td>High (%)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>4</td>
<td>23±2</td>
<td>5±2</td>
<td>0</td>
<td>Normal (%)</td>
</tr>
<tr>
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<td>Low (%)</td>
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<tr>
<td></td>
<td>Christlieb</td>
<td>25</td>
<td>47±4</td>
<td>25±2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*H/N/L shift in plasma renin activity: p<0.001

Values are mean±SD. IDDS, insulin-dependent diabetic subjects; I, initial study values of youth-onset IDDS; II, follow-up study values of youth-onset IDDS; Christlieb, values reported by Christlieb et al (Reference 16) for adult-onset IDDS.
High PRA in adult diabetic subjects has been reported in association with elevated GFR, but this association was lacking in the present study. Hyperplasia and increased renin production of juxtaglomerular, afferent, and efferent arteriolar cells, induced by captopril or diuretic therapy and renal ischemia or thrombotic angiopathy, cannot explain the high PRA found among these young IDDS.

Low PRA, common among older diabetic subjects with nephropathy or neuropathy, has been explained on the basis of sclerosed cells or decreased sympathetic stimulation of the juxtaglomerular cells. In the present study, low PRA was present in IDDS with normal AER or mildly elevated AER (group 2) and normal serum creatinine levels. Sympathetic activity was normal in the majority of low renin subjects, and the prevalence of abnormal sympathetic activity was similar among IDDS with high, normal, or low PRA.

The spectrum of high, normal, and low levels of PRA noted in the young IDDS may be an expression of the autoimmune process active in youth-onset diabetic subjects. The juxtaglomerular renin-producing cells are endocrine in nature. Autoantibodies against endocrine cells of the anterior pituitary, thyroid, parathyroid, and adrenal glands, gastric mucosa, and pancreatic islets have been identified in youth-onset IDDS and may appear simultaneously. Early phases of heightened activity in autoimmune diseases have been described for pancreatic β cells, anterior pituitary cells, and thyroid cells. The decline in PRA over 5 years in the young cohort together with the absence of high PRA in adult IDDS is compatible with an initial phase of hyperactivity of the juxtaglomerular renin-producing cells followed by a gradual or sudden decline of activity. If diabetic nephropathy is a consequence of an autoimmune process, it raises the possibility that the phenomenon occurs independently of the diabetic state, a common finding among autoimmune disorders associated with insulin-dependent diabetes. The recent finding of an increased rate of sodium-lithium countertransport in red blood cells, a marker of risk for essential hypertension, in IDDS with but not without nephropathy suggests that high-renin hypertension, or a subset, may be the independent expression of the autoimmune process striking renin-producing cells of the juxtaglomerular apparatus.

Increased activity of the renin-angiotensin system in the present study is reflected in the heightened RVR and its significant association with high FF, elevated AER, and PRA. Mesangial cells and efferent arterioles have receptors for Ang II and are highly sensitive to its constrictive action while afferent arterioles are not. High FF reflects the postglomerular constriction that is occurring. Infusion of renin in rabbits induces protein excretion, and Ang II infusion increases fractional clearance of polyanionic dextran sulfate, a reliable marker of albumin filtration. When Ang II production in diabetic rats is blocked with the converting enzyme inhibitor enalapril, glomerular structural injury and proteinuria do not develop as in untreated rats, thus implicating pressure and not metabolic changes.

In the present study intrarenal pressure as reflected in heightened RVR did not correlate with other parameters of renal hemodynamics measured in the IDDS, that is, GFR and ERPF.

AER were significantly associated with glycemic control as reflected in Hb A₁ and with RVR, indicating that lowering AER may reflect either improved glycemic control or reduced intrarenal capillary pressure, or both. However, glycemic control was not associated with PRA or RVR, suggesting that improved metabolic control that results in a reduction in AER does not affect intrarenal pressure. Of the three parameters of renal hemodynamics measured in this study, GFR, ERPF, and RVR, only RVR was significantly associated with AER.

Increased vasoactivity induced by exercise among IDDS in groups 3 and 4 may be analogous to the heightened cardiovascular sensitivity to Ang II and norepinephrine secondary to increased body sodium noted in normotensive and hypertensive adult IDDS. Increases in body sodium may already be occurring in teenagers and may be secondary to enhanced renin-angiotensin-aldosterone activity.

Development of diabetic nephropathy among youth-onset IDDS is significantly higher among those with onset of diabetes between 0 and 10 years of age than among those with onset after the age of 10. All subjects in the cohort who initially had clinical proteinuria or developed it in the 5 years of observation had the onset of diabetes close to 5 years of age. Their prepubertal duration of 6–7 years is significantly longer than the 2.5 years of those who continued to have normal or elevated AER after 5 years and is considerably longer than the 0.5 years of the four subjects in the initial study who had normal AER and low PRA. It is suggested, therefore, that the risk of diabetic nephropathy in youth-onset IDDS is directly related to the prepubertal duration of diabetes, the height of PRA reached prepubertally, and the time course of its postpubertal decline. The frequency and intensity of stimulation of renin stores and the resulting Ang II levels are likely to be important factors determining risk.

Longitudinal studies of PRA among prepubertal subjects from the time of onset of clinical diabetes are indicated to ascertain the risk for developing diabetic nephropathy. Measures initiated during puberty to reduce high-renin activity may prevent or ameliorate the process leading to nephropathy.

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