Renal Abnormalities in Normotensive Insulin-Dependent Diabetic Offspring of Hypertensive Parents

Thierry P. Hannedouche, Luis-Paulo Marques, Svetlozar Natov, Alvimar G. Delgado, Christian Boitard, Bernard Lacour, and Jean-Pierre Grunfeld

To assess the effects of genetic predisposition of essential hypertension on early renal function in recent insulin-dependent diabetics, we studied inulin, para-aminom hippuric acid, sodium, and lithium clearances in 69 unselected diabetics with (n=20) and without (n=49) a family history of essential hypertension. Despite similar metabolic control, glomerular filtration rate and mean arterial pressure were significantly higher in diabetics with than in those without a family history of hypertension. However, no difference was found between the two groups regarding renal vascular resistance, sodium excretion, or fractional proximal and distal sodium reabsorption. Renal responses to acute captopril (75 mg) administration were evaluated in 27 patients (six with family history of hypertension). Captopril decreased filtration fraction and mean arterial pressure similarly in both groups, whereas glomerular filtration rate and renal vascular resistance decreased more dramatically in diabetics with family history of hypertension. These findings indirectly suggest an abnormal response to angiotensin of vascular tone in recent diabetics with familial predisposition to hypertension. Renal response to acute nicardipine (2.5 mg i.v.) administration was analyzed in 24 patients (five with family history of hypertension). In both groups, nicardipine similarly decreased mean arterial pressure and renal vascular resistance and induced a marked natriuretic effect due to a predominant reduction in proximal reabsorption of sodium. However, the increase in sodium excretion was twofold to threefold more pronounced in diabetics with a family history of hypertension. Whether these early renal abnormalities may contribute to the risk of diabetic nephropathy, as suggested by retrospective studies, remains to be determined. (Hypertension 1992;19:378-384)

KEY WORDS • diabetes, insulin-dependent • essential hypertension • diabetic nephropathies • genetic hypertension • glomerular filtration rate • sodium • calcium channel blockers • angiotensin converting enzyme inhibitors

Diabetic nephropathy is the most serious complication of insulin-dependent diabetes (IDD), responsible for a 10-fold excess of cardiovascular mortality due to end-stage renal failure and hypertension. It develops in 30–40% of IDD patients; the risk peaks during the second decade of diabetes and declines thereafter.1,2 Hypertension in IDD patients develops mainly in connection with the clinical emergence of nephropathy, whereas those in whom nephropathy does not develop remain normotensive despite the longer duration of diabetes and advancing age.3

Why some but not all IDD patients are susceptible to diabetic nephropathy has not been determined. Besides poor glycemic control, renal hemodynamic changes and hypertension may play an important role.4,5 Of note, an elevation of blood pressure has been observed before any sign of impairment of renal function, and the presence of genetic hypertension accelerates nephropathy in streptozotocin diabetic rats.6,7 Inherited predisposition to hypertension was proposed to increase the susceptibility to nephropathy in IDD since nondiabetic parents of IDD patients with nephropathy have higher blood pressure than the parents of IDD patients without nephropathy.8–10 and sodium-lithium countertransport (Na+/Li+ CT) is increased in patients with IDD before the onset of nephropathy and is associated with hyperfiltration.11 Similarly, nondiabetic subjects genetically predisposed to hypertension were found to have higher velocity of erythrocyte Na+/Li+ CT than normotensive controls without familial history of hypertension, and it has been suggested that these abnormalities in red blood cell Na+/Li+ CT may be a marker of enhanced renal proximal tubular reabsorption in essential hypertension.12–16

Since genetic predisposition to essential hypertension may be a factor predisposing to diabetic nephropathy, possibly through inherited dysregulation of membrane ion transport or vascular tone as in essential hypertension,17–23 we evaluated in the present study whether a familial history (FH) of hypertension could influence renal hemodynamics, sodium excretion, and tubular handling in the very early stage of diabetes. The response of renal hemo-
dynamics and renal sodium handling to acute calcium channel blockade and acute converting enzyme inhibition was further assessed using acute nicardipine and captopril administration, respectively.

Methods

Sixty-nine Caucasian patients (44 men), aged 28±1 years, participated in this study after informed consent was obtained. All patients were type 1 diabetics in whom diagnosis was established according to the World Health Organization criteria. These patients were part of a ongoing study of the determinants of early diabetic glomerular hyperfiltration and constituted a homogeneous group, with a mean diabetes duration of 42 days (range, 7–180 days) and short-term insulin therapy of 9±1 days. None of these diabetics had hypertension or diabetic nephropathy. Other main characteristics of these patients are indicated in Table 1.

First degree relatives were invited to have fasting plasma glucose determination and blood pressure measurement by their practitioner. When blood pressure measurements were not available in all relatives or data were insufficient, patients were not considered for the study. Diabetic patients were divided into two groups according to the presence (FH+, n=20) or the absence (FH−, n=49) of FH of essential hypertension. FH+ was defined as patients having nonobese and nondiabetic first degree relatives under 60 years of age with diastolic blood pressure greater than 95 mm Hg, mean arterial pressure greater than 117 mm Hg, or receiving antihypertensive treatment. Most relatives were considered hypertensive because they had been receiving antihypertensive therapy.

All patients were investigated in the metabolic ward while on a controlled sodium diet of 90–120 mmol/24 hr. None of the subjects was taking drugs other than insulin. Subjects were studied after correction of hyperglycemia by conventional insulin therapy; blood glucose levels were below 9 mmol/l (±0.5 mmol/l), as estimated by the mean of six consecutive determinations during each clearance procedure. Since para-aminohippuric (PAH) clearance may be underestimated due to glucose-PAH adduct formation or lithium clearance overestimated in relation to osmotic diuresis, the absence of ketone and glucose was carefully verified in all urine samples for each patient. The evening before the clearance studies, each participant was given 750 mg lithium carbonate orally to estimate lithium concentrations ranging from 0.20 to 0.25 mmol/l. Clearances were performed in the morning, after overnight fasting, as previously described using a constant rate infusion of inulin (polyfructosein, Inutest, Laevosan, Linz, Austria) and PAH (Nephrotest, Biologische Arbeitsgemeinschaft GmbH, Lich, FRG) during six consecutive clearance periods of 30 minutes each. Urine was collected every 30 minutes by spontaneous voiding, and blood specimens were drawn at the beginning and the end of each collection period. At the end of period 3, sublingual administration of 75 mg captopril was given as a single dose to 27 patients (six FH+, 21 FH−) and intravenous nicardipine (2.5 mg) was infused to 24 patients (five FH+, 19 FH−). Mean arterial pressure (MAP) was measured using a noninvasive oscillometric technique (Dinamap, Critikon, Tampa, Fla., cuff size 23×13 cm) every 10 minutes during clearance evaluation.

Laboratory Procedures

Hematocrit (Ht) was assessed by routine Coulter counter (Coulter Electronics, Hialeah, Fla.). Plasma and urine concentration of inulin and PAH were determined using a Technicon Autoanalyzer I (Technicon Instrument Corp., Tarrytown, N.Y.), plasma sodium by Astra 8 (Beckman Instruments Inc., Fullerton, Calif.), urine sodium by SMA II autoanalyzer (Technicon), plasma and urine lithium by atomic absorption spectrophotometry (PU 9000, PYE Unicam Ltd, Cambridge, England), and plasma glucose on Hitachi 717 (Hitachi Ltd, Tokyo). Mean values in normal subjects matched for age and sex are 126±16 (mean±SD) for inulin clearance and 710±145 ml/min (mean±SD) for PAH clearance (n=20).

Concentrations of serum angiotensin converting enzyme (ACE) activity were determined before and 60 minutes after captopril administration. After collection, blood samples were ultracentrifuged and serum was kept frozen at −80°C until assayed using an enzymatic kinetic method modified from the method of Cushman and Cheung. Normal values in our laboratory are 21.5±5.4 nmol/min/ml (mean±2 SD).

Calculations and Statistics

Clearances were calculated according to standard clearance formula

\[ C = \frac{UV}{P} \]

where \( U \) is urine concentration of the substance, \( V \) is urine flow, and \( P \) is its plasma concentration, and were adjusted for a body surface of 1.73 m². The average of three 30-minute clearance determinations of inulin or PAH was calculated to evaluate glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively. MAP was calculated as the average of all 10-minute measurements during clearance procedure. Renal vascular resistance (RVR) was calculated as

\[ RVR = \frac{MAP \times (1-Ht)}{ERPF} \]

and filtration fraction (FF) as

\[ FF = \frac{GFR}{ERPF} \]
Segmental tubular sodium handling was determined using lithium clearance as an index of absolute proximal
escape. Fractional proximal reabsorption of lithium (FPR\textsubscript{Li}) was calculated as

\[ FPR_{\text{Li}} = 1 - \left( C_{\text{Li}} / \text{GFR} \right) \]

where \( C_{\text{Li}} \) is clearance of lithium, and fractional distal reabsorption of sodium (FDR\textsubscript{Na}) was calculated as

\[ FDR_{\text{Na}} = 1 - (C_{\text{Na}} / C_{\text{Li}}) \]

where \( C_{\text{Na}} \) is clearance of sodium. Other values were calculated as follows: absolute proximal isoosmotic reabsorption (APR)

\[ \text{APR} = \text{GFR} - C_{\text{Li}} \]

absolute distal sodium reabsorption (ADR\textsubscript{Na})

\[ \text{ADR}_{\text{Na}} = (C_{\text{Li}} - C_{\text{Na}}) \times P_{\text{Na}} \times 10^{-3} \]

where \( P_{\text{Na}} \) is the plasma sodium concentration; and fractional excretion of sodium (FEN\textsubscript{Na})

\[ \text{FEN}_{\text{Na}} = C_{\text{Na}} / \text{GFR} \]

All results were expressed as mean±SEM unless otherwise stated. Statistical analysis was performed using a multivariate model of analysis of variance to compare values in FH+ and FH− groups (SYSTAT statistical software, SYSTAT Inc., Evanston, Ill.) and using analysis of variance for repeated measurements to compare the effects of either captopril or nicardipine in the two subgroups of patients according to familial history of hypertension. Differences were considered as significant at the 0.05 level.

**Results**

The IDD patients studied here had a short duration of diabetes and insulin therapy and had achieved relatively good metabolic control. Average blood glucose was 6.3±0.3 mmol/l, glycated hemoglobin (HbA\textsubscript{1c}) 11.7±0.5%, and no patients were glycosuric or ketonuric. Baseline GFR and ERPF for the whole group were 136±2 and 715±18 ml/min • 1.73 m\textsuperscript{2}, respectively; these values were nearly normal and did not differ between FH+ and FH− groups. Besides poor metabolic control, renal hemodynamic changes and hypertension could play an impor-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FH− (n=49)</th>
<th>FH+ (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min • 1.73 m\textsuperscript{2})</td>
<td>132±3</td>
<td>145±5*</td>
</tr>
<tr>
<td>ERPF (ml/min • 1.73 m\textsuperscript{2})</td>
<td>680±20</td>
<td>709±32</td>
</tr>
<tr>
<td>FF</td>
<td>0.199±0.005</td>
<td>0.209±0.01</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>86.4±1.3</td>
<td>92.4±4*</td>
</tr>
<tr>
<td>RVR (dyne • sec • cm\textsuperscript{-2})</td>
<td>6,367±207</td>
<td>6,635±455</td>
</tr>
<tr>
<td>FE\textsubscript{Na} (x 10\textsuperscript{-3})</td>
<td>16±1</td>
<td>14±2</td>
</tr>
<tr>
<td>U\textsubscript{Na} • V (mmol/min • 1.73 m\textsuperscript{2})</td>
<td>0.307±0.019</td>
<td>0.288±0.041</td>
</tr>
<tr>
<td>FPR\textsubscript{Li}</td>
<td>0.760±0.009</td>
<td>0.754±0.009</td>
</tr>
<tr>
<td>APR (ml/min • 1.73 m\textsuperscript{2})</td>
<td>101±3</td>
<td>108±4</td>
</tr>
<tr>
<td>FDR\textsubscript{Na} (mmol/min • 1.73 m\textsuperscript{2})</td>
<td>0.929±0.005</td>
<td>0.94±0.009</td>
</tr>
<tr>
<td>ADR\textsubscript{Na} absolute distal sodium reabsorption rate (mmol/min • 1.73 m\textsuperscript{2})</td>
<td>4.13±0.15</td>
<td>4.72±0.25*</td>
</tr>
</tbody>
</table>

FH−, without family history of hypertension; FH+, with family history of hypertension; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; MAP, mean arterial pressure; RVR, renal vascular resistance; FEN\textsubscript{Na}, fractional sodium excretion; U\textsubscript{Na} • V, urinary sodium excretion; FPR\textsubscript{Li}, fractional proximal reabsorption of sodium; APR, absolute proximal isoosmotic reabsorption; FDR\textsubscript{Na}, fractional distal sodium reabsorption rate; ADR\textsubscript{Na}, absolute distal sodium reabsorption rate.

In the 27 patients given a single dose of captopril (75 mg), serum ACE activity decreased dramatically (from 27.3±7.4 to 3.1±2.4 nmol/min/ml; \( p<0.001 \)) indicating nearly complete inhibition of angiotensin II formation in the serum and presumably within the kidney as well. In both FH+ and FH− patients, captopril induced a significant decrease in FF \(( p<0.001 \)) and RVR \(( p<0.01 \)), whereas ERPF was unchanged (Table 3 and Figure 1). GFR decreased only in FH− diabetics from 145±5 to 127±5 ml/min • 1.73 m\textsuperscript{2} \(( p<0.05 \)) and similarly in FH+ and FH− groups (Table 4 and Figure 2). Nicardipine induced a significant natriuretic effect, probably related to a decrease in FPR\textsubscript{Li} \(( p<0.001 \)) and APR \(( p<0.05 \)) and, to a lesser extent, in FDR\textsubscript{Na}. U\textsubscript{Na} • V and FEN\textsubscript{Na} despite a slight but significant decrease in FPR\textsubscript{Li} and APR \(( p<0.01 \)). ADR\textsubscript{Na} and FDR\textsubscript{Na} were unchanged by captopril.

In the 24 patients given acute low dose of nicardipine (25 mg), acute calcium channel blockade significantly decreased FF \(( p<0.05 \)) in FH− group and MAP \(( p<0.001 \)) and RVR \(( p<0.01 \)) in both groups, whereas GFR decreased and ERPF increased nonsignificantly and similarly in FH+ and FH− groups (Table 4 and Figure 2). Nicardipine induced in both groups a significant natriuretic effect, probably related to a decrease in FPR\textsubscript{Li} \(( p<0.001 \)) and APR \(( p<0.05 \)) and, to a lesser extent, in FDR\textsubscript{Na}. U\textsubscript{Na} • V and FEN\textsubscript{Na} tended to decrease more markedly in FH− diabetics (40%, FH+ versus 16%, FH−; and 42%, FH+ versus 12%, FH−, respectively), but the interaction groups x treatment was not significant.

**Discussion**

Diabetic nephropathy develops in approximately 30–40% of IDD patients after 10–15 years of diabetes duration. Besides poor metabolic control, renal hemodynamic changes and hypertension could play an impor-
significantly affected by captopril. Decrease induced by captopril (interaction captopril x family history) was significantly and fractional reabsorption of lithium (FRU) (p<0.01) were diabetics. RPF, renal plasma flow; FENa, fractional excretion of sodium.

![Figure 1](https://hyper.ahajournals.org/)

**Figure 1.** Distribution plot shows changes in renal hemodynamics and segmental sodium reabsorption before and after captopril administration in diabetic patients with (FH+) or without (FH−) a familial history of essential hypertension. Glomerular filtration rate (GFR) in FH− diabetics (p<0.05), filtration fraction (FF) (p<0.001), mean arterial pressure (MAP) (p<0.05), renal vascular resistance (RVR) (p<0.01), and fractional reabsorption of lithium (FRLi) (p<0.01) were significantly affected by captopril. Decrease induced by captopril (interaction captopril x family history) was significantly more marked for GFR in FH− diabetics and for RVR in FH+ diabetics. RPF, renal plasma flow; FENa, fractional excretion of sodium.

![Figure 2](https://hyper.ahajournals.org/)

**Figure 2.** Distribution plot shows changes in renal hemodynamics and segmental sodium reabsorption before and after nicardipine administration in diabetic patients with or without a family history of essential hypertension. Changes induced by nicardipine were significant for filtration fraction (FF) (p<0.05), mean arterial pressure (MAP) (p<0.01), renal vascular resistance (RVR) (p<0.01), and fractional lithium reabsorption (FRLi) (p<0.001). No interaction nicardipine x condition was found. GFR, glomerular filtration rate; RPF, renal plasma flow.

### Table 3. Effects of Acute Captopril (75 mg sublingually) Administration on Renal Hemodynamics and Segmental Tubular Handling of Sodium in Insulin-Dependent Diabetic Patients With or Without a Family History of Essential Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FH− (n=21)</th>
<th>FH+ (n=6)</th>
<th>p&lt;0.05</th>
<th>p&lt;0.01</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min • 1.73 m²)</td>
<td>−8.9±2.7*</td>
<td>0.1±7.1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ERPF (ml/min • 1.73 m²)</td>
<td>−4.4±3</td>
<td>15±8.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF</td>
<td>−12.5±1.8†</td>
<td>−12.3±3.3†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>−2.8±1.5†</td>
<td>−7.6±3.8*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVR (dyne • sec • cm⁻²)</td>
<td>−5.5±2.9*</td>
<td>−18.3±4.1‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FENa (x10⁻²)</td>
<td>22.2±12.1</td>
<td>27.6±26.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UN • V (mmol/min • 1.73 m²)</td>
<td>10.3±10.9</td>
<td>29.8±38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPRL,</td>
<td>−3.1±11‡</td>
<td>−3.9±1.3‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APR (ml/min • 1.73 m²)</td>
<td>−11.8±3.2‡</td>
<td>−6.8±7.6‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRN, (mmol/min • 1.73 m²)</td>
<td>0±0.5</td>
<td>0.1±0.9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ADRN, absolute distal sodium reabsorption rate</td>
<td>3.4±2.3</td>
<td>6.4±8.1</td>
<td></td>
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</tr>
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</table>

### Table 4. Effects of Acute Nicardipine (2.5 mg i.v.) Administration on Renal Hemodynamics and Segmental Tubular Handling of Sodium in Insulin-Dependent Diabetic Patients With or Without a Family History of Essential Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FH− (n=19)</th>
<th>FH+ (n=5)</th>
<th>p&lt;0.05</th>
<th>p&lt;0.01</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min • 1.73 m²)</td>
<td>−1.5±2.6</td>
<td>−4.3±6.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERPF (ml/min • 1.73 m²)</td>
<td>8.5±4.8</td>
<td>3.2±5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF</td>
<td>−6.1±2.8*</td>
<td>7.7±3.2*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>−6±1.7†</td>
<td>−5.4±3.6†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVR (dyne • sec • cm⁻²)</td>
<td>−11.8±3.2†</td>
<td>−7.8±5.1†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FENa (x10⁻²)</td>
<td>23.5±7.4*</td>
<td>57.2±28.4*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UN • V (mmol/min • 1.73 m²)</td>
<td>23.7±8.1*</td>
<td>48±24.6*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPRL,</td>
<td>−3.6±0.9‡</td>
<td>−4.3±1.1‡</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>APR (ml/min • 1.73 m²)</td>
<td>−3.2±2.3*</td>
<td>−8.3±7*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRN,</td>
<td>−0.2±0.6</td>
<td>−1±0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRN, absolute distal sodium reabsorption rate</td>
<td>10.5±3.9*</td>
<td>8.9±5.6*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Blood pressure was found to increase before any sign of diabetic nephropathy. Of note, blood pressure was found to increase before any sign of diabetic nephropathy.
of these features may be shared with nondiabetic subjects genetically predisposed to hypertension, who were found in some but not all reports to have greater GFR and 24-hour urinary output, lower plasma renin activity and urinary kallikrein excretion,17-25 and higher velocity of erythrocyte Na⁺-Li⁺ CT than FH– normotensive controls.12-16 These findings may be due to an abnormality in renal tubular handling of ions and water17-19 since the velocity of erythrocyte Na⁺-Li⁺ CT may be positively correlated with FPRu, and presumably with greater sodium proximal reabsorption.14 However, in IDD as well as in essential hypertensive patients, the links between these abnormalities have not been definitely settled.

In this homogeneous group of recent IDD patients receiving a normal sodium diet and with relatively good metabolic control, we found a slightly albeit significantly higher GFR and MAP in FH+ diabetic patients. Although differences in MAP were slight, it should be noted that blood pressure values represented the average of repeated 10-minute measurements with an automatic device, therefore probably minimizing bias due to "white coat" or to investigator. Higher GFR and MAP have been similarly reported in nondiabetic offspring of essential hypertensive parents.18,25 In contrast, renal plasma flow and FF were not significantly different in FH+ and in FH– diabetics as reported in some20-22 but not all18,33 studies in nondiabetic offspring of essential hypertensive parents. In our diabetic patients, both absolute and fractional excretion of sodium and lithium were unaffected by a familial history of essential hypertension, whereas APR was slightly but nonsignificantly increased in FH+ IDD patients. Contrasting with an initial report,14 recent studies using standardized protocols of lithium clearance measurement (controlled sodium diet, supine position) have indicated that with either normal or high sodium diet, the normotensive nondiabetic offspring of hypertensive parents have normal or even decreased proximal tubular reabsorption of sodium.35,36 However, with high sodium supplementation, blood pressure tended to be slightly higher in FH+ patients, whereas sodium excretion and sodium proximal escape were unchanged35 or increased.36 There may be several explanations for the different renal sodium handling in FH+ or FH– IDD patients. First, some of the discrepancies may be related to sample bias since certain studies enrolled a small number of selected subjects. Second, the diabetic state per se may be confounding because of persistent mild hyperglycemia and ensuing volume expansion37 due to osmotic shift of glucose and to increased proximal sodium reabsorption,38 probably through stimulation of sodium-glucose cotransport.39 Indeed, FPRu, and presumably of sodium was significantly increased when compared with our normal control values.40,41 These results raised the question of the validity of the measurement of the erythrocyte Na⁺-Li⁺ CT as a marker of Na⁺-H⁺ antiporter activity in epithelial cells of the renal tubule. In the proximal tubule, the Na⁺-H⁺ antiporter has been found to account only for approximately 40% of the active transport of sodium.42 Moreover, the relation between erythrocyte Na⁺-Li⁺ CT and epithelial Na⁺-H⁺ antiporter has been questioned because the Na⁺-H⁺ exchange in the human and rabbit proximal renal brush border is amiloride sensitive, whereas in both species Na⁺-Li⁺ CT could not be inhibited by amiloride under a variety of conditions.43 Insulin resistance and hyperinsulinism are common features in essential hypertension44 and have been shown to increase renal sodium reabsorption and vascular reactivity through stimulation of certain membrane ion transport systems, particularly the Na⁺-K⁺- ATPase and the Na⁺-H⁺ exchange systems.45,46 In diabetics, high systemic hyperinsulinism and ensuing stimulation of ion transport systems may partially offset the influence of genetic polymorphism of proximal sodium reabsorption, Na⁺-H⁺ exchange, or both.

A subgroup of essential hypertensive patients with normal or elevated plasma renin activity fail to appropriately increase renal blood flow with increased dietary sodium or conversely to appropriately decrease renal blood flow in response to angiotensin II infusion while on high sodium diet, whereas this abnormal renal response was reversible after short-term converting enzyme inhibition.21 Of note, recent evidence has been produced that a large fraction (greater than 80%) of these patients, termed "non-modulators," are FH+ and FH–.24,25 Furthermore, a familial aggregation of non-modulation was evidenced, and renal and adrenal features characteristic of non-modulation were found in normotensive subjects with non-modulating hypertensive first degree relatives.26,27 These results suggest that non-modulation may be an inheritable trait and that abnormalities of the control of renal vascular tone may precede essential hypertension.

In the present study, acute administration of captopril induced a significant decrease in FF, MAP, and RVR and an increase in ERPF in both FH+ and FH– groups of diabetics. Although some difference in the response between groups could have been missed because of the small number of FH+ patients, the decrease in RVR was higher in FH+ than in FH– patients with IDD, and RVR in FH+ patients with IDD decreased after captopril to levels similar to baseline RVR in FH– patients with IDD. Similar findings have been reported in normotensive FH+ subjects in comparison with FH– normotensive subjects.20 This suggests that renal vascular tone in subjects genetically predisposed to hypertension is partly dependent on excessive renal angiotensin II formation. In diabetics, this abnormality of renal angiotensin may be blunted due to increased plasma volume and exchangeable sodium.37

After captopril, GFR decreased slightly but significantly in FH–, whereas it was unchanged in FH+. A similar decrease in GFR was found in healthy FH– normotensive subjects.40 Contrasting with reports in essential hypertensive and normotensive subjects,40,47 captopril did not induce a natriuretic effect in IDD patients, irrespective of a familial history of hypertension, despite a slight but significant decrease in FPRu and APRu. The natriuretic effect of captopril is prominently related to reduced proximal reabsorption, and in IDD patients the angiotensin II–dependent component of sodium proximal reabsorption and its suppression by ACE inhibitor may be blunted by enhanced sodium-glucose cotransport.

Calcium channel blockers have been reported to induce marked renal vasodilation predominantly in the afferent arteriolar resistance.48,49 In our study and as in nondiabetic normotensive subjects,41 an acute low dose
of nicardipine induced a significant decrease in MAP, RVR, and to a lesser extent in FF in both FH− and FH+ groups of diabetics, whereas GFR and ERPF were practically unchanged. In normotensive subjects, the administration of either diltiazem or nifedipine, at doses that do not decrease blood pressure, induced a higher increase in renal blood flow and presumably a larger decrease in RVR in normotensive FH+ subjects.23,24 Since these results have not been observed with ntspecific vasodilators such as nitroprusside or acetylcholine, these observations have been interpreted as evidence for a primary defect in calcium-dependent control of the renovascular smooth muscle.23 However, since the diltiazem-induced increase in renal blood flow was demonstrated only in sodium-restricted diet, it has been speculated that the enhanced effects of diltiazem on renal blood flow may primarily be due to suppression of the angiotensin II–mediated component of renal vascular tone.25 In both FH+ and FH− patients with IDD, nicardipine nonsignificantly increased renal plasma flow, whereas it decreased markedly RVR and blood pressure to a similar extent in both groups. The lack of change in ERPF in our experiment may be merely related to the profound decrease in arterial pressure after nicardipine, which due to counterregulating mechanisms, may offset the increase in ERPF as previously found in animals.50

Calcium channel blockers consistently exert a potent natriuretic effect in animals and normotensive and hypertensive humans51,52 even when GFR and renal plasma flow are prevented from increasing either by an aortic clamp53 or after intrarenal infusion of a low dose of the drug.54 This natriuretic effect was shown to be related to a decrease in both proximal and distal tubular reabsorption of sodium, probably by directly interfering with sodium transport along the renal tubule.55 In diabetics, nicardipine induced a similar marked natriuretic effect, essentially due to a decrease in proximal reabsorption of sodium. Of note, changes in sodium excretion were even more pronounced (twofold to threefold higher) in FH+ than in FH− IDD patients.

In conclusion, recent patients with IDD, offspring of nondiabetic essential hypertensive parents, exhibit a pattern of renal abnormalities including an increase in GFR and MAP, whereas RVR and sodium excretion were nonsignificantly increased and decreased, respectively. In accordance with recent reports in normotensive offspring of essential hypertensive parents, fractional proximal reabsorption calculated using lithium clearance was not altered in FH+ diabetics, although values in the whole group were higher than in nondiabetic controls. Acute calcium channel blockade or ACE inhibition induced rather similar responses in FH+ and FH− groups. Since the changes in GFR and blood pressure were quantitatively minor, it remains to be determined whether these renal abnormalities may influence the late renal outcome in diabetics as suggested by retrospective studies.

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References

Renal abnormalities in normotensive insulin-dependent diabetic offspring of hypertensive parents.
T P Hannedouche, L P Marques, S Natov, A G Delgado, C Boitard, B Lacour and J P Grünfeld

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