Renal Responses to Sodium Restriction in Patients with Early Diabetes Mellitus

JUDITH A. MILLER
Department of Medicine, University of Toronto, Toronto, Canada.

Abstract. Increased GFR and decreased renal vascular resistance are common renal hemodynamic changes in persons with early, uncomplicated, insulin-dependent diabetes mellitus. It has been hypothesized that excess total-body sodium in patients with diabetes contributes to the renal vasodilation, possibly by suppressing vasoconstricting neurohormonal systems. This study was undertaken to examine whether sodium restriction could normalize these renal abnormalities. Subjects were 12 male patients with uncomplicated insulin-dependent diabetes mellitus (duration, <5 yr). Results were compared with those of an age- and gender-matched control group. All subjects received either a high-sodium diet (200 mmol/day) or a sodium-restricted diet (20 mmol/day) for 7 days, according to a randomized crossover protocol. GFR and RPF were measured using inulin and para-aminohippurate clearance techniques, respectively. Subjects with diabetes were maintained euglycemic during the clearance measurements. GFR was significantly higher in the diabetic group than in the control group with sodium repletion (124 ± 4 versus 107 ± 8 mL/min/1.73 m²; P = 0.03), and renal vascular resistance was significantly reduced (94 ± 6 versus 107 ± 17 mm Hg/L/min; P = 0.05). In response to sodium restriction, the hematocrit increased significantly in both groups, as did PRA and aldosterone, although responses in the diabetic group were somewhat blunted, indicating persisting volume expansion. Despite this humoral activation, sodium restriction had little effect on renal hemodynamic function in control subjects. In the diabetic subjects, this maneuver appeared to exacerbate the underlying renal abnormalities, with the GFR increasing to 131 ± 4 mL/min/1.73 m² (P = 0.05) and the renal vascular resistance declining to 73 ± 5 mm Hg/L/min (P = 0.001). These data indicate that, rather than correcting renal hyperperfusion, sodium restriction exacerbates these characteristic abnormalities, suggesting that mechanisms other than suppression of vasoconstrictor activity are operative in the underlying renal hemodynamic abnormalities of early, uncomplicated, insulin-dependent diabetes mellitus. (J Am Soc Nephrol 8: 749-755, 1997)
the renal hemodynamic abnormalities characteristic of IDDM. Little direct evidence exists that sodium restriction can modify renal hemodynamic function in diabetic human patients.

The aim of these experiments was, therefore, to examine the hypothesis that sodium restriction could alleviate the classical renal hemodynamic abnormalities of early IDDM. It was hypothesized that sodium restriction, which is known to stimulate both renal sympathetic nerve activity (21) and the renin/angiotensin system (19), would modify the increased GFR and RPF, thereby lending support to the theory that the renal vasodilation characteristic of early IDDM is related to the suppression of vasoconstrictor systems by excess total-body sodium.

The experiments presented here were designed as a randomized crossover study to examine the renal responses to sodium restriction in diabetes. The subjects were young male patients with early uncomplicated IDDM, within 5 yr of diagnosis. A group of age- and gender-matched control subjects was similarly studied. Renal hemodynamic function was assessed with standard inulin and para-aminohippurate (PAH) clearance techniques.

Materials and Methods

Subjects

Twelve male patients with early IDDM (duration, 2.8 ± 0.4 yr), of mean age 23 ± 2 yr, were recruited for the study. Seven of the 12 diabetic subjects and 8 of the 10 control subjects had participated in a previous study by this laboratory (17); therefore, the characteristics were similar to those in that study. That is, the diabetic subjects were otherwise healthy, normotensive, and nonobese, receiving no medications except for insulin, and without complications, including retinopathy, microalbuminuria, and signs of autonomic neuropathy, as determined by a qualified internist. The glycosylated hemoglobin level was <10% for all diabetic subjects. The 10 control subjects were healthy, nonobese, normotensive, male subjects receiving no medications. All subjects were nonsmokers. The study was performed with the approval of the University of Toronto Human Subjects Review Committee and with the informed written consent of each subject.

Each diabetic subject was studied on two occasions, i.e., after a 7-day period on a 200-mmol sodium-containing diet and after a 7-day period on a 20-mmol sodium-containing diet. The diets were prepared by the research dietitian to contain 1 g/kg-day protein and to conform to the Canadian Diabetic Association recommendations for diabetic diets. The sequence was randomly determined. The studies were separated by a minimum of 2 weeks, during which time the subjects ingested their normal diet. Twenty-four-hour urine sodium, potassium, and urea excretion were measured on both the sixth and seventh days before the study day, to ensure compliance. The prestudy preparation was identical for the control subjects.

The diabetic subjects were admitted to the Clinical Investigation Unit of the Toronto Hospital the evening before the study day and were maintained euglycemic during the night and throughout the study by a closed-loop insulin delivery system (1,17,22). On the day of the testing, the volunteer subjects reported to the Human Renal Physiology Laboratory. All studies were conducted at 8:30 a.m., after an overnight fast, with the subjects lying supine in a warm quiet room.

Study Protocol

Each control subject had two 18-gauge, peripheral venous cannulas inserted into antecubital veins, one for infusion of inulin and PAH and one (in the opposite arm) for blood sampling. The diabetic subjects had an additional cannula inserted for insulin infusions. All patients voided and then drank 800 mL of water in the first 45 min, to induce water diuresis. Two hundred milliliters of water were ingested in each hour of the protocol, to maintain an adequate urine output for collection of spontaneously voided samples. Blood pressure and heart rate were recorded throughout the clearance periods (Dinamap Vital Signs Monitor 1846SX, Critikon, Ontario, Canada). In the diabetic subjects, plasma glucose levels were measured every 30 min by the glucose oxidase method (Beckman Glucose Analyzer II; Beckman Instruments Corp., Fullerton, California). Euglycemia was maintained throughout the clearance periods with minor adjustments in the insulin infusion rate. For all subjects, renal hemodynamics were measured using inulin and PAH clearance techniques. After collection of blood and urine samples as inulin blanks, a priming infusion containing 25% inulin (60 mg/kg) and 20% PAH (8 mg/kg) was administered. Thereafter, inulin and PAH were infused continuously at a rate calculated to maintain their plasma concentrations constant at 20 and 1.5 mg/dL, respectively. After a 90-min equilibration period, three timed urine collections of 20-min duration each were obtained by spontaneous voiding with the subject remaining in the supine position. The inulin and PAH clearance results as well as the values for sodium and osmolality from the final two urine collections were averaged, and the mean values represented the GFR and RPF results. At the end of this period, blood samples were drawn for PRA, aldosterone, plasma norepinephrine (PNE), sodium, osmolality, and hematocrit (HCT) determinations.

Blood samples collected for inulin and PAH determinations were immediately centrifuged at 3000 rpm for 10 min at 4°C. Plasma was separated, placed on ice, and then stored at −70°C before the assay. Urine samples collected from diabetic subjects for inulin and PAH determination were promptly alkalinized by addition to 4 mL of urine of 23 μL of 4 M NaOH, to prevent formation of an adduct between PAH and glucose (23). Samples for PRA were collected and prepared in the same manner. PRA was determined by the quantitation of Ang I generation by radioimmunoassay, using a New England Nuclear kit. Aldosterone was measured by radioimmunoassay, using the Coat-A-Count system (Diagnostic Products Corporation, Los Angeles, CA). PNE was measured by HPLC with electrochemical detection (24).

Serum sodium concentrations were measured by an ion-selective electrode method and urine sodium by a flame photometry method. Inulin concentrations in plasma and urine were measured by a modified method of Walser et al. (25) and PAH concentration by a spectrophotometric method of Brun (26). The inulin and PAH clearances, corrected for body surface area, represented GFR and RPF, expressed per 1.73 m², respectively. Filtration fraction (FF) represented the ratio of GFR to RPF. RBF was calculated by dividing the RPF by (1 − HCT). Renal vascular resistance (RVR) was derived by dividing mean arterial pressure (MAP) by RBF and is expressed as millimeters of Hg per liter per minute.

Statistical Analyses

Results are presented as mean ± SE. Renal hemodynamic and excretory data and HCT, MAP, PNE, PRA, and aldosterone levels were analyzed by using paired t tests to examine within-subject differences between diets. Unpaired t tests were used to examine between-group differences between diabetics and normal controls in their responses to sodium restriction.

Results

Baseline Measurements

The baseline results of body weight, 24-h urine sodium, urine sodium excretion, potassium and urea excretion, MAP,
heart rate, and HCT with the two diets are shown in Table 1. In summary, after 7 days of sodium restriction, there were significant reductions in body weight, 24-h urine sodium, and urine sodium excretion. There were significant increases in HCT in both groups in response to sodium restriction. MAP and heart rate did not change in response to diet in either group. Urea excretion did not change significantly in response to diet in either group, indicating that protein intake was equivalent for the two diet regimens. Potassium excretion also was not altered significantly between the diets. The plasma insulin level in the control group was 19 ± 7 pM, and that in the diabetic group was 104 ± 22 pM ($P = 0.0001$ versus control group). Insulin was infused at an average rate of 0.5 ± 0.001 U/h in the diabetic group with sodium repletion, in an average volume of 58 ± 2 mL iv fluid/14 h. With the sodium-restricted diet the average insulin requirement was 0.6 ± 0.01 U/h, and the average amount of fluid infused was 64 ± 2 mL/14 h. The mean plasma glucose level achieved throughout the study was 5.2 ± 0.1 mM in the diabetic subjects and 4.7 ± 0.2 mM in the control group ($P = $ not significant). Plasma insulin levels, insulin requirements, and plasma glucose levels did not differ significantly between diets.

**Humoral Effects of Sodium Restriction**

Responses of PRA, aldosterone and PNE to the sodium-restricted diet are illustrated in Figure 1. There were significant increases in PRA and aldosterone in both groups, but the extent of the increases in the diabetic group was significantly less than that in the control group. In summary, PRA in the control group was 0.37 ± 0.08 ng Ang I/L/s during sodium-replete conditions and increased to 0.86 ± 0.1 ng Ang I/L/s ($P = 0.01$ versus sodium replete) during sodium restriction. In the diabetic group, the PRA was 0.22 ± 0.02 ng Ang I/L/s ($P = 0.03$ versus control group) during sodium-replete conditions and increased to 0.48 ± 0.1 ng Ang I/L/s ($P = 0.01$ versus sodium replete; $P = 0.04$ versus control group) during sodium restriction. The aldosterone level was 138 ± 19 pM in the control group with sodium repletion and increased to 642 ± 98 pM ($P = 0.002$ versus sodium replete) during sodium restriction. In the diabetic group, the aldosterone level was 113 ± 18 pM.

![Figure 1. Hormonal responses to sodium restriction.](image)

Table 1. Baseline measures

<table>
<thead>
<tr>
<th></th>
<th>Sodium-Replete</th>
<th>Sodium-Restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Diabetic</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>84 ± 3</td>
<td>80 ± 2</td>
</tr>
<tr>
<td>Na$^+$ excretion (mmol/day)</td>
<td>212 ± 8</td>
<td>201 ± 10</td>
</tr>
<tr>
<td>UNaV$^b$ (μmol/min)</td>
<td>330 ± 56</td>
<td>254 ± 34</td>
</tr>
<tr>
<td>K$^+$ excretion (mmol/day)</td>
<td>74 ± 9</td>
<td>59 ± 7</td>
</tr>
<tr>
<td>Urea excretion (mmol/day)</td>
<td>377 ± 12</td>
<td>358 ± 8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>82 ± 4</td>
<td>80 ± 1</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>56 ± 6</td>
<td>63 ± 5</td>
</tr>
<tr>
<td>HCT</td>
<td>0.399 ± 0.001</td>
<td>0.389 ± 0.005</td>
</tr>
</tbody>
</table>

$^a$ $P \leq 0.05$, compared with sodium-replete conditions.

$^b$ UNaV, urine sodium excretion; HR, heart rate.
(P = not significant versus control group) during sodium-replete conditions and increased to 314 ± 22 pM (P = 0.005 versus sodium replete; P = 0.01 versus control group) with sodium restriction. In the control subjects, PNE was 0.75 ± 0.1 nM during sodium-replete conditions and 0.94 ± 0.1 nM with sodium restriction (P = 0.05 versus sodium replete). In the diabetic group, the PNE was 0.6 ± 0.1 nM (P = not significant versus control group) during sodium-replete conditions and 0.6 ± 0.2 nM (P = not significant versus sodium replete; P = not significant versus control group) with sodium restriction.

Renal Hemodynamic Effects of Sodium Restriction

The GFR, RBF, and RVR responses to sodium restriction are shown in Figure 2. Individual GFR, RBF, and RVR results for the diabetic subjects are depicted in Table 2. In summary, in the control group, during sodium-replete conditions, GFR was 107 ± 8 mL/min/1.73 m², RPF was 579 ± 71 mL/min/1.73 m², RBF was 977 ± 125 mL/min/1.73 m², FF was 0.20 ± 0.02, and RVR was 107 ± 17 mm Hg/L/min. In response to the sodium-restricted diet, the control group GFR, RPF, RBF, FF, and RVR were not significantly affected, with values of 102 ± 8 mL/min/1.73 m², 603 ± 46 mL/min/1.73 m², 1015 ± 83 mL/min/1.73 m², 0.17 ± 0.008, and 90 ± 6 mm Hg/L/min, respectively.

In the diabetic group during sodium-replete conditions, the GFR was significantly augmented, compared with the control group (124 ± 4 mL/min/1.73 m²; P = 0.05 versus control), and the RVR was significantly reduced (94 ± 6 mm Hg/L/min; P = 0.05 versus control). RPF was 656 ± 89 mL/min/1.73 m² (P = not significant versus control), RBF was 1075 ± 148 mL/min/1.73 m² (P = not significant versus control), and FF was 0.22 ± 0.02 (P = not significant versus control). Ingestion of the sodium-restricted diet exerted a significant effect on renal hemodynamic function in the diabetic group. GFR was significantly increased by this maneuver (131 ± 4 mL/min/1.73 m²; P = 0.05 versus sodium replete; P = 0.03 versus control group response). RPF increased to 765 ± 66 mL/min/1.73 m²; P = 0.005 versus sodium replete; P = 0.08 versus control group response). RBF increased to 1261 ± 113 mL/min/1.73 m² (P = 0.003 versus sodium replete; P = not significant versus control group response). FF fell to 0.18 ± 0.01 (P = 0.005 versus sodium replete; P = not significant versus control group response). RVR decreased to 73 ± 5 mm Hg/L/min (P = 0.001 versus sodium replete; P = 0.05 versus control group response).

Discussion

These studies were designed to determine whether the ingestion of a sodium-restricted diet could modify the renal hemodynamic abnormalities in human patients with early uncomplicated IDDM. The rationale for proceeding with this study was twofold. It is known that sodium restriction increases renal sympathetic nerve activity and the renin secretion rate in normal human subjects (21) and renal Ang II content in streptozotocin-induced diabetic rats (19), leading to the hypothesis that this maneuver would alleviate the state of renal vasodilation in human diabetes. In addition, two studies have examined the renal responses to sodium restriction in the streptozotocin/rat model, with conflicting results (18,19). The author is unaware of any studies addressing this issue in human diabetic patients.

The key findings in this study were that (1) profound sodium restriction resulted in an increase in HCT, PRA, and aldosterone and a decrease in weight in both groups; (2) responses were blunted in the diabetic group (approximating values measured in the unrestricted control subjects), indicating a continuing degree of volume expansion; (3) sodium restriction did not significantly affect renal hemodynamic function in control subjects, although RVR appeared numerically reduced by this maneuver; and, (4) rather than reducing the GFR and RBF to levels found in the unrestricted control subjects, sodium restriction resulted in an exacerbation of the underlying renal hemodynamic abnormalities in the diabetic group.
that a sodium-restricted diet significantly augmented both renal norepinephrine spillover and the renin secretion rate in normal human subjects. Although one might speculate that such activation of neurohormonal vasoconstricting systems might alter renal hemodynamic function, available studies of the renal responses to sodium restriction in both animals and human subjects do not confirm this. In work by Schor et al. (30), Munich-Wistar rats subjected to chronic dietary salt restriction exhibited a significant decrease in glomerular plasma flow but maintenance of GFR through augmentation of glomerular capillary pressure. In a study by Bank et al. (18), normal rats exposed to sodium restriction showed no significant change in RPF or GFR. Vallon et al. (19) were unable to demonstrate a significant change in renal hemodynamic function in normal rats fed low-sodium and -salt diets, in spite of increases in kidney tissue Ang II levels. In the study by Friberg et al. (21), even though there were elevations in renal vein concentrations of PNE and PRA, RVR was not increased and in fact was numerically, although not significantly, reduced. Those authors, as well as others (30), speculate that this phenomenon occurs because of activation of counter-regulatory vasodilating systems. In this study, consistent with the aforementioned experimental data, sodium restriction had little effect on renal hemodynamic function in normal subjects. RBF was numerically, but not significantly increased, and there was a small nonsignificant decline in RVR.

However, the renal hemodynamic response to sodium restriction in the diabetic subjects was striking. During sodium-replete conditions, the GFR was significantly elevated, compared with control subjects, although not in the range traditionally designated as "hyperfiltration," and the RVR was significantly reduced. In the study by Bank et al. (18), it was speculated that this characteristic pattern of renal hyperperfusion could be attributed to a suppression of renin/angiotensin system activity by excess total-body sodium. Using the streptozotocin/rat model of diabetes, those investigators demon-

### Table 2. Renal hemodynamic responses in diabetic subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>RBF (ml/min/1.73 m²)</th>
<th>RVR (mm Hg/L/min)</th>
<th>FF</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>RBF (ml/min/1.73 m²)</th>
<th>RVR (mm Hg/L/min)</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB²</td>
<td>117</td>
<td>844</td>
<td>93</td>
<td>0.22</td>
<td>115</td>
<td>965</td>
<td>93</td>
<td>0.19</td>
</tr>
<tr>
<td>GB</td>
<td>136</td>
<td>978</td>
<td>80</td>
<td>0.22</td>
<td>131</td>
<td>1214</td>
<td>67</td>
<td>0.18</td>
</tr>
<tr>
<td>GC</td>
<td>110</td>
<td>1048</td>
<td>84</td>
<td>0.17</td>
<td>154</td>
<td>1406</td>
<td>57</td>
<td>0.17</td>
</tr>
<tr>
<td>MD²</td>
<td>117</td>
<td>522</td>
<td>159</td>
<td>0.37</td>
<td>124</td>
<td>679</td>
<td>111</td>
<td>0.29</td>
</tr>
<tr>
<td>MH</td>
<td>118</td>
<td>720</td>
<td>124</td>
<td>0.29</td>
<td>123</td>
<td>936</td>
<td>86</td>
<td>0.22</td>
</tr>
<tr>
<td>AM</td>
<td>139</td>
<td>1128</td>
<td>74</td>
<td>0.20</td>
<td>142</td>
<td>1296</td>
<td>64</td>
<td>0.18</td>
</tr>
<tr>
<td>JT²</td>
<td>147</td>
<td>2512</td>
<td>35</td>
<td>0.10</td>
<td>154</td>
<td>2263</td>
<td>39</td>
<td>0.12</td>
</tr>
<tr>
<td>WC²</td>
<td>103</td>
<td>860</td>
<td>106</td>
<td>0.20</td>
<td>111</td>
<td>1210</td>
<td>73</td>
<td>0.15</td>
</tr>
<tr>
<td>HJ</td>
<td>119</td>
<td>1220</td>
<td>70</td>
<td>0.16</td>
<td>129</td>
<td>1460</td>
<td>57</td>
<td>0.15</td>
</tr>
<tr>
<td>KS</td>
<td>123</td>
<td>904</td>
<td>105</td>
<td>0.22</td>
<td>126</td>
<td>1114</td>
<td>86</td>
<td>0.18</td>
</tr>
<tr>
<td>SD²</td>
<td>116</td>
<td>733</td>
<td>127</td>
<td>0.25</td>
<td>120</td>
<td>1111</td>
<td>83</td>
<td>0.18</td>
</tr>
<tr>
<td>DN</td>
<td>144</td>
<td>1430</td>
<td>68</td>
<td>0.16</td>
<td>150</td>
<td>1475</td>
<td>65</td>
<td>0.171</td>
</tr>
</tbody>
</table>

*Initial sodium-restricted diet.*

Total exchangeable sodium is increased in diabetic animals (15) and human patients (14) in the absence of intrinsic renal disease, whereas actual intravascular volume has been reported to be increased in some studies (15) but not in others (16). An increase in absolute and fractional proximal tubular reabsorption of sodium and water has been documented in diabetic human patients by using the lithium clearance technique (20). The mechanism is unknown, but it has been suggested that increased proximal sodium reabsorption may be mediated by stimulation of the glucose/sodium cotransporter, with resultant parallel absorption of glucose and sodium (27,28), or by the sodium-resorptive effect of hyperinsulinemia (29). Although this study was not designed to examine abnormalities in sodium excretion, it was noted that diabetic subjects receiving a low-sodium diet were able to reduce sodium excretion to the same extent as control subjects, despite a probable increase in tubular sodium load because of increased GFR, indicating avid sodium reabsorption. Additional evidence of sodium conservation is provided by the fact that sodium restriction increased the plasma concentrations of PRA and aldosterone only to the values exhibited by unrestricted control subjects, suggesting that, although some volume contraction did occur, it was not to the same extent as that exhibited by the restricted control group. Therefore, it is apparent that even profound sodium restriction is not completely effective in overcoming the stimulus to volume expansion in diabetic subjects. However, hormonal parameters appear to remain somewhat sensitive to physiologic regulatory factors.

The renal hemodynamic response to sodium restriction in the control subjects deserves comment. It has been shown by different investigators that sodium restriction activates neurohormonal vasoconstricting systems. In a study by Vallon et al. (19), using Munich-Wistar rats, salt and sodium restriction increased kidney tissue Ang II levels. Friberg et al. (21), in a study that used norepinephrine kinetics to estimate renal sympathetic nerve activity in normal human subjects, demonstrated...
strated that the abnormally elevated glomerular blood flow and GFR could be ameliorated by a sodium-restricted diet. The hyperfiltration state was restored by the administration of saralasin, providing evidence that this correction of renal vasodilation had occurred via stimulation of the renin/angiotensin system secondary to a sodium restriction-mediated reduction in extracellular fluid volume. This renal vasoconstricting response was not apparent in the diabetic human patients taking part in this study. Although profound sodium restriction in these subjects was able to increase renin/angiotensin aldosterone activity, at least to the level found in unrestricted control subjects, glomerular hyperfiltration was actually exacerbated by this maneuver. The reasons for these disparities are unclear, but differences in species, diet, prestudy preparation, duration of diabetes, and blood glucose levels probably all contributed. These results appear to support the findings of Vallon et al. (19), wherein rats with experimental diabetes exhibited exacerbation of the underlying renal hemodynamic abnormalities with salt restriction, despite an increase in kidney tissue Ang II levels. The mechanism was unknown, but those authors speculated that sodium restriction possibly increased renal prostaglandin production or aggravated the normally enhanced proximal tubular sodium reabsorption in the diabetic rats, ultimately reducing distal delivery and tubuloglomerular feedback activity and increasing pregglomerular vasodilatation. The results from this study of whole-kidney function in human subjects cannot offer any information that would clarify which of these putative mechanisms are operative. More sophisticated studies using the renal norepinephrine spillover technique would be required to examine the function of renal nerves and the intrarenal renin/angiotensin system in diabetic subjects. The possibility exists that a vasoconstricting response to sodium restriction was not observed in the diabetic subjects because the stimulus did not result in a sufficient reduction in extracellular fluid volume. Although volume was not directly measured, it was apparent from changes in humoral parameters that the volume status of the two groups was not comparable at the end of the sodium restriction period. However, it was also evident from the HCT values and the measures of renin/angiotensin system activity that some volume contraction did occur. One might speculate that, if volume expansion were playing an important role in modulating renal hemodynamic function, any reduction should result in a decline in GFR, at least to the level of the unrestricted control subjects. In a previous study from this laboratory (17), sodium restriction in diabetic subjects resulted in a significant reduction in central venous pressure and a consequent restoration of the normal vasoconstrictor response to baroreceptor deactivation in the peripheral vasculature. That the renal circulation appears to respond to a similar degree of volume contraction differently from the peripheral circulation, with a decrease in vascular resistance rather than an increase, suggests either renal unresponsiveness or enhanced counter-regulatory vasodilating system activity. Taken together, these results do not support an important role for volume expansion in the maintenance of glomerular hyperfiltration in diabetic human subjects. There were other potential factors in this study that could have influenced the results. It is known that protein intake (5) and glycemia (31–33) can affect renal hemodynamic function. However, the protein content of the diets was similar for all subjects and the 24-h urea excretion was unchanged after both periods. Therefore, differences in protein intake can be excluded as a confounding variable. In addition, patient selection allowed the author to exclude diabetic subjects with inadequate glucose control, defined as glycosylated hemoglobin levels of >10%, and all diabetic subjects were maintained strictly euglycemic throughout the clearance procedures. It was decided to study only male patients because several of the hormones involved in sodium homeostasis are affected by the menstrual cycle (34). Because MAP did not appear to be significantly affected by sodium intake in either group, the change in RVR in response to sodium restriction appeared to be the result not of casual variations in blood pressure but of actual alterations in RBF. Although plasma insulin concentrations differed between the two groups, it is unlikely that this interfered with the results. Studies that have used the hyperinsulinemic clamp technique to examine the renal hemodynamic responses to insulin in normal subjects have found little effect (29). In studies with human diabetic patients, insulin infusions have resulted in small decreases in GFR (35). In addition, insulin infusions have been shown to activate the sympathetic nervous system in both normal subjects and diabetic patients (36,37), leading one to expect renal vasoconstriction rather than vasodilation. Most importantly, there were no differences in plasma insulin concentrations or in the amount of insulin required to maintain euglycemia between diets. Therefore, it is unlikely that any of these factors (proteín intake, glycemia, insulin levels, or gender) could have contributed to the observed results. In summary, this study demonstrates that (1) profound sodium restriction results in a humoral response that is similar in normal subjects and patients with early uncomplicated IDDM; (2) humoral responses to sodium restriction are blunted in diabetic subjects (approximating values found in unrestricted control subjects), indicating avid sodium conservation and continuing volume expansion; and (3) the renal response to sodium restriction is qualitatively different in diabetic subjects, who seem to respond with an increase in GFR and RBF, whereas control subjects exhibit little change. These results suggest that mechanisms other than suppression of neurohumoral vasoconstrictor system activity are operative in the diabetic hyperfiltration state. Further studies are required to determine the mechanism for this phenomenon, which presently remains obscure. Acknowledgments Portions of this work were presented at the American Society of Nephrology meeting, San Diego, California, October 1995, and published in abstract form (38). This work was supported by Grant 92–27 from the Physicians of Ontario through the Physicians’ Services Inc. Foundation. J. A. Miller was the recipient of a Research Scholarship from the Kidney Foundation of Canada. The author gratefully acknowledges Ms. Julie Dionne for her expert technical assistance in the Renal Physiology Laboratory and the staff nurses of the Clinical Investigation Unit of the Toronto Hospital for their assistance with this protocol.
References


