Effects of insulin on renal interstitial hydrostatic pressure and natriuretic response to volume expansion in diabetic rats

Daiyi Tang, Tianzheng Yu, and Ali A. Khrabi

Department of Physiological Sciences, Eastern Virginia Medical School, Norfolk, Virginia 23501

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Tang, Daiyi, Tianzheng Yu, and Ali A. Khrabi. Effects of insulin on renal interstitial hydrostatic pressure and natriuretic response to volume expansion in diabetic rats. Am J Physiol Regul Integr Comp Physiol 286: R751–R755, 2004. First published December 4, 2003; 10.1152/ajpregu.00561.2003.—Diabetes mellitus (DM) is characterized by alterations in fluid balance and blood volume homeostasis. Renal interstitial hydrostatic pressure (RIHP) has been shown to play a critical role in mediating sodium and water excretion under various conditions. The objective of this study was to determine the effects of immediate and delayed initiation of insulin treatment on the restoration of the relationship between RIHP, natriuretic, and diuretic responses to acute saline volume expansion (VE) in diabetic rats. Diabetes was induced by an intraperitoneal injection of streptozotocin (STZ; 65 mg/kg body wt). Four groups of female Sprague-Dawley rats were studied: normal control group (C), untreated diabetic group (D), immediate insulin-treated diabetic group (DI; treatment with insulin for 2 wk after STZ injection), and delayed insulin-treated diabetic group (DDI; treatment with insulin for 2 wk after STZ injection). RIHP and sodium and water excretions were measured before and during VE (5% body wt/30 min) in the four groups of anesthetized rats. VE significantly increased RIHP, fractional excretion of sodium (FENa), and urine flow rate (V) in all groups of rats. Basal RIHP, RIHP response to VE (ΔRIHP), and FENa and V responses to VE (ΔFENa and ΔV) were significantly lower in the D group compared with the C group of rats. ΔRIHP was significantly higher in both DI and DDI groups compared with D group but was similar to that of the C group of rats. While in the DI group the ΔFENa response to VE was restored, ΔFENa was significantly increased in DDI compared with D group, but it remained lower than that of the C group. In conclusion, insulin treatment initiated immediately after the onset of diabetes restores basal RIHP and RIHP, natriuretic, and diuretic responses to VE; however, delayed insulin treatment restores the basal RIHP and RIHP response to VE but does not fully restore the natriuretic response to VE.

Diabetes mellitus (DM) is characterized by alterations in fluid balance and blood volume homeostasis. In diabetic rats, the natriuretic and diuretic responses to volume expansion (VE) are significantly attenuated compared with those of control nondiabetic rats (16–18, 22). An increase in renal sympathetic nerve activity has been suggested to play an important role in the blunted natriuretic and diuretic responses to VE in the diabetic state (17, 18). Insulin treatment has been shown to reverse, at least in part, the increased renal sympathetic nerve activity and restore the renal excretory responses to VE in diabetic rats (17, 18, 22). Although these data demonstrate a reversal of the increased renal sympathetic nerve activity by insulin treatment in diabetic rats, the intrarenal mechanism(s) that are responsible for the restoration of the natriuretic and diuretic responses to VE by insulin treatment in diabetic rats remains unclear.

The kidneys are the main organ system regulating sodium and water balance, and renal interstitial hydrostatic pressure (RIHP) plays an important role in determining the rate of the tubular reabsorption of sodium and water, and consequently in mediating sodium and water excretion (4, 6, 10). Various physiological and pharmacological maneuvers that increase RIHP are associated with increases in sodium excretion (4, 6, 10). The results of a recent study by Patel and Carmines (16) suggested that, during the early stages of diabetes, a reduced RIHP response to VE may be responsible for the impaired natriuretic and diuretic responses in diabetic rats. Although the effects of insulin treatment on the natriuretic and diuretic responses to acute VE are well studied (17, 18), the possible effects of insulin treatment, initiated at different times of the diabetic state, on the renal responses, especially RIHP response to VE, are not well understood. In this study we tested the hypothesis that in diabetic rats the restoration of the natriuretic and diuretic responses to VE, by immediate or delayed initiation of insulin treatment, is mediated by normalization of the RIHP response to VE.

In diabetic patients, tight glycemic control is a critical factor in providing maximal protection against cardiovascular events and the deterioration of renal function (7, 13, 19). Insulin replacement is the most likely therapy to achieve and maintain levels of glycemia that are likely to prevent and/or delay long-term complications in patients with diabetes (12, 20). Although the diagnosis and the initiation of therapy in diabetic patients may depend on a variety of factors, it is clear that insulin treatment is initiated at different stages of the disease in different diabetic patients. Therefore, the purpose of the present study was to establish the relationship between RIHP and natriuretic and diuretic responses to VE in STZ-induced diabetic rats and to determine the role of insulin treatment, initiated at different times of the diabetic state (2 days and 2 wk after STZ injection), on RIHP and natriuretic and diuretic responses to VE. Furthermore, lithium and phosphate were utilized as indexes of proximal tubule reabsorption (1, 21). Fractional excretion of lithium (FEli) and fractional excretion of phosphate (FEP) were determined during control and VE periods in all rats studied.

METHODS

All rats in these studies were female Sprague Dawley (SD), purchased at 11–12 wk of age from Harlan Sprague Dawley (Indianapolis, IN). All rats were fed a normal Purina Rat Chow containing...
0.1 meq sodium/g and had free access to water. All protocols in this study were conducted in accordance with the National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committee at Eastern Virginia Medical School.

Polyethylene Matrix Implantation

The implantation procedure of the polyethylene (PE) matrix has been previously described (9). RIHP was measured directly and continuously via a PE matrix that was implanted in the left kidney of rats when they were 12–13 wk old (9) and weighed 200–280 g.

Induction of DM

Diabetes was induced by an intraperitoneal injection of 65 mg/kg body wt of streptozotocin (STZ, Pharmacia and Upjohn, Kalamazoo, MI). STZ was diluted in 0.1 mol/l citrate buffer (pH = 4.0). Normal control rats were given an equivalent amount of citrate buffer. Diabetes was diagnosed 2 days after STZ injection by measuring the blood glucose (BG) concentration from the cut tip of the tail by the glucose oxidase technique using One Touch II blood glucose meter (Lifescan, Milpitas, CA). Only rats that received STZ injection and had a BG concentration >15 mmol/l were included in the diabetic groups of rats (14).

Four groups of female SD rats were studied in these experiments. Normal control group (n = 7). Normal control group (C) of rats were normal control nondiabetic female SD rats that did not receive insulin treatment.

Untreated diabetic group (n = 7). Untreated diabetic group (D) of rats were diabetic female SD rats that did not receive insulin treatment.

Diabetes + immediate insulin treatment group (n = 6). Diabetes + immediate insulin treatment group (DI) of rats were diabetic rats that received immediate daily NPH human insulin (Eli Lilly, Indianapolis, IN) treatment. Insulin was injected subcutaneously at a dose of 3 U/100 g adjusted individually to control BG concentration within normal glycemic range. Insulin treatment was initiated when diabetes was confirmed and continued daily at about the same time of the day (~3:00 PM) for a period of 2 wk.

Diabetes + delayed insulin treatment group (n = 8). Diabetes + delayed insulin treatment group (DDI) of rats were diabetic rats that received delayed daily (~3:00 PM) NPH human insulin treatment. Insulin was injected subcutaneously at a dose of 3 U/100 g adjusted individually to control BG concentration within normal glycemic range. Insulin treatment was initiated 2 wk after STZ injection and continued for a period of 2 wk.

Surgical Procedure for VE Experiments

On the day of the acute experiment, rats were anesthetized with Inactin (100 mg/kg), and catheters were placed in the trachea (PE-240) and left jugular vein (PE-50) for intravenous infusion of 1.5 ml/100 g body wt⁻¹ h⁻¹ of saline with 6 mM LiCl and 1.5 ml/100 g body wt⁻¹ h⁻¹ of a solution of 3% inulin and 6.25% bovine albumin in saline (with 6 mM LiCl). A PE-90 catheter was implanted in the left carotid artery for mean arterial pressure (MAP) measurement and blood withdrawal. A PE-90 catheter with a flared tip was placed in the bladder for urine collection. The rats were allowed 1 h to recover after completion of the surgical procedures. Then a control period of 30 min was started. During the 30-min clearance period, MAP and RIHP were measured and recorded continuously. At the end of this period ~1 ml of blood was withdrawn from the left carotid artery for plasma electrolytes, lithium, and inulin measurements. At this time VE (5% body wt saline in 30 min) was started. Urine was collected for 20 min starting 10 min after the initiation of VE. Again, during the second clearance period, MAP and RIHP were measured and recorded continuously. At the end of this period, ~1 ml of blood was withdrawn from the left carotid artery for plasma electrolytes, lithium, and inulin measurements. All rats were killed by air embolism at the end of the experiment while still under deep anesthesia, and both kidneys were excised and weighed. This method of euthanasia is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association.

Analyses

Glomerular filtration rate (GFR) was calculated from the clearance of inulin, and inulin concentrations were measured by the anthrone method (3). Sodium and lithium concentrations in plasma and urine were measured using flame photometry (Instrumentation Laboratory model 943, Lexington, MA). Phosphate concentrations in plasma and urine were measured according to the method of Chen et al. (2).

Statistical Analyses

Statistical analyses were performed using SPSS 10.0 statistical software (SPSS, Chicago, IL). The data were analyzed with standard paired Student’s t-tests for comparisons between the first and second clearance periods in the same group or with a one-way ANOVA, followed by a post hoc Bonferroni correction for multiple group comparisons at equivalent periods. All data are means ± SE, and P < 0.05 was accepted as a statistically significant difference.

RESULTS

The average body weight, kidney weight, and BG concentration in all groups are summarized in Table 1. BG concentration was significantly elevated in D rats compared with C rats. Despite having similar body weights on the day of STZ or vehicle injection, D rats weighed significantly less than C rats, but they exhibited marked renal hypertrophy with greater kidney weight as well as kidney weight/body weight ratio on the day of the terminal acute experiment. Insulin treatment restored the BG levels to normal in DI and DDI rats. Kidney weight and kidney weight/body weight ratio were significantly lower in DI and DDI rats compared with D rats (Table 1). Compared with C rats, basal GFR was significantly lower in D rats but was not significantly different in DI rats (Table 2).

| Table 1. Body weight, blood glucose, kidney weight, kidney weight/body weight ratio in normal control, untreated diabetic, diabetic + immediate insulin treatment, and diabetic + delayed insulin treatment groups of female Sprague-Dawley rats |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | C (n = 7)        | D (n = 7)        | DI (n = 6)       | DDI (n = 8)      |
| Initial body wt, g | 265.4±5.1       | 268.0±4.9       | 251.5±6.6        | 253.4±4.9        |
| Final body wt, g  | 280.4±3.7†      | 238.3±6.0†      | 291.0±5.9†       | 291.0±5.5‡       |
| Blood glucose, mmol/l | 4.6±0.3†       | 26.1±0.8        | 4.2±0.4‡        | 4.2±0.4‡ |
| Kidney wt, g       | 1.90±0.05†      | 2.43±0.12       | 2.07±0.06†‡      | 2.23±0.03*        |
| Kidney wt/body wt, × 100 | 0.68±0.02†     | 1.02±0.04       | 0.71±0.01†‡      | 0.77±0.01†‡       |

Values are means ± SE; n, no. of rats; DI, diabetic + immediate insulin treatment group; *P < 0.05 vs. normal control group (C); †P < 0.05 vs. untreated diabetic group (D); ‡P < 0.05 vs. diabetic + delayed insulin treatment group (DDI).
Basal RIHP was significantly lower in D rats compared with C rats. VE resulted in significant increases in RIHP, V, FENa, FELi, and FEpi in all groups of rats (Table 2). As shown in Fig. 1, ΔRIHP was significantly lower for D (1.6 ± 0.3 mmHg) rats compared with C (5.2 ± 0.6 mmHg), DI (4.3 ± 0.5 mmHg), and DDI (4.6 ± 0.4 mmHg) rats. There were no significant differences in basal RIHP and ΔRIHP among C, DI, and DDI groups of rats (Table 2 and Fig. 1). As shown in Figs. 2 and 3, ΔV, ΔFENa, ΔFELi, and ΔFEpi were significantly lower in D (104.1 ± 27.0 μl/min, 3.5 ± 0.5%, 21.8 ± 3.6%, 13.0 ± 1.4%, respectively) group compared with C (368.3 ± 39.9 μl/min, 12.4 ± 1.4%, 44.7 ± 5.8%, 25.6 ± 2.2%, respectively) group of rats. With insulin treatment, ΔV, ΔFENa, ΔFELi, and ΔFEpi were significantly increased in DI (353.9 ± 40.2 μl/min, 12.9 ± 2.6%, 37.4 ± 6.2%, 27.4 ± 4.8%, respectively) and DDI (371.9 ± 38.4 μl/min, 8.7 ± 0.5%, 25.1 ± 2.9%, 17.4 ± 2.0%, respectively) rats compared with untreated D (104.1 ± 27.0 μl/min, 3.5 ± 0.5%, 21.8 ± 3.6%, 13.0 ± 1.4%, respectively) group of rats (Figs. 2 and 3). When compared with C group, ΔFENa, ΔFELi, and ΔFEpi were similar in DI group but were significantly lower in DDI group of rats (Figs. 2 and 3).

**DISCUSSION**

Consistent with the results of a previous study by Patel and Carmines (16), the results of the present study show that basal RIHP and the increase in RIHP that is associated with natriuresis and diuresis responses to VE were reduced in STZ-induced diabetic rats. The results of the present study also show that restoration of BG levels to normal by immediate or delayed insulin treatment results in the normalization of basal RIHP and RIHP response to VE; however, the natriuretic (ΔFENa) and the reduction in proximal tubule reabsorption responses (as evaluated by ΔFELi and ΔFEpi) are restored by delayed insulin treatment (DDI).

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Table 2. *Renal responses to acute saline volume expansion (5% body wt/30 min) in normal control, untreated diabetic, diabetic + immediate insulin treatment, and diabetic + delayed insulin treatment groups of female Sprague-Dawley rats*

<table>
<thead>
<tr>
<th>Group</th>
<th>Period</th>
<th>C (n = 7)</th>
<th>D (n = 7)</th>
<th>DI (n = 6)</th>
<th>DDI (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>Control</td>
<td>131.6 ± 1.3</td>
<td>121.1 ± 2.3*</td>
<td>132.4 ± 6.5</td>
<td>113.7 ± 8.2*</td>
</tr>
<tr>
<td>RIHP, mmHg</td>
<td>VE</td>
<td>5.2 ± 0.7†</td>
<td>10.4 ± 1.0††</td>
<td>2.7 ± 0.4</td>
<td>4.3 ± 0.5*</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>Control</td>
<td>2.52 ± 0.11†</td>
<td>2.75 ± 0.23</td>
<td>1.71 ± 0.30</td>
<td>3.09 ± 0.33*</td>
</tr>
<tr>
<td>V, μl/min</td>
<td>VE</td>
<td>68.8 ± 14.1</td>
<td>437.1 ± 51.5††</td>
<td>65.1 ± 10.3</td>
<td>169.3 ± 29.5*</td>
</tr>
<tr>
<td>FENa, %</td>
<td>Control</td>
<td>2.8 ± 0.4†</td>
<td>15.2 ± 1.7††</td>
<td>1.2 ± 0.3</td>
<td>4.7 ± 0.9*</td>
</tr>
<tr>
<td>FELi, %</td>
<td>VE</td>
<td>27.6 ± 5.5</td>
<td>72.3 ± 9.3††</td>
<td>24.6 ± 3.6</td>
<td>46.5 ± 4.9*</td>
</tr>
<tr>
<td>FEpi, %</td>
<td>Control</td>
<td>10.5 ± 4.1</td>
<td>36.0 ± 2.6††</td>
<td>9.9 ± 2.3</td>
<td>22.9 ± 2.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. VE, volume expansion; MAP, mean arterial pressure; RIHP, renal interstitial hydrostatic pressure; GFR, glomerular filtration rate; V, urine flow rate; FENa, fractional excretion of sodium; FELi, fractional excretion of lithium; FEpi, fractional excretion of phosphate. *P < 0.05 between control and VE periods in the same group of rats. †P < 0.05 vs. D group. ††P < 0.05 vs. DI treatment group. §P < 0.05 vs. C group at equivalent periods.

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Fig. 1. Changes in renal interstitial hydrostatic pressure (ΔRIHP) in response to volume expansion (VE) in normal control (C), untreated diabetic (D), diabetic + immediate insulin treatment (DI), and diabetic + delayed insulin treatment (DDI) groups of female Sprague-Dawley rats. †Significant difference compared with untreated diabetic (D) group of rats using a 1-way ANOVA, followed by a post hoc Bonferroni correction.

Fig. 2. Changes in fractional excretion of sodium (ΔFENa) and urine flow rate (ΔV) in response to VE in normal control, untreated diabetic, diabetic + immediate insulin treatment, and diabetic + delayed insulin treatment groups of female Sprague-Dawley rats. †Significant difference compared with untreated diabetic group of rats using a 1-way ANOVA, followed by a post hoc Bonferroni correction. §Significant difference compared with normal control group of rats using a 1-way ANOVA, followed by a post hoc Bonferroni correction.
immediate initiation of insulin treatment but not by delayed insulin treatment in diabetic rats.

The kidneys regulate sodium and water balance through a combination of intrinsic and extrarenal mechanisms. Small changes in RIHP have been shown to have a significant effect on sodium excretion in normal rats under various physiological conditions (4, 6, 8, 10). Increases in RIHP reduce sodium reabsorption by the proximal tubule and loop of Henle during VE (5). When RIHP is prevented from increasing, the natriuretic response to VE is suppressed (5, 11). The exact mechanism of how increases in RIHP are translated to decreases in sodium reabsorption and increases in sodium excretion is not known. However, several mechanisms to explain these relationships have been previously suggested. These mechanisms include an increase in the back-leak of fluid and solutes into the proximal tubule and/or increases in medullary blood flow and consequently medullary washout as a result of increases in RIHP, which would ultimately result in a decrease in sodium reabsorption and an increase in sodium excretion (9, 10, 16). In the present study, basal RIHP, increases in RIHP, and the natriuretic and diuretic responses to VE were diminished in diabetic rats (Table 2, Figs. 1 and 2). Correction of the hyperglycemia by immediate insulin treatment (DI group) restored basal RIHP and RIHP response to VE and completely reversed the attenuated natriuretic and diuretic responses to VE that have been reported to occur in untreated diabetic rats (16) and that are observed in this study (D group). These data suggest that, in the early stages of diabetes, the reduced RIHP response to VE is responsible, at least in part, for the blunted natriuretic and diuretic responses to VE. Immediate insulin treatment initiated at the onset of diabetes appears to restore the natriuresis and diuresis response to VE by restoring the RIHP response to VE.

It is important to note that, although correction of the hyperglycemia by delayed insulin treatment (DDI group) normalized the basal RIHP and RIHP response to VE, it did not totally restore the natriuretic response to VE in diabetic rats. These data suggest that in the early stage of diabetes, the reduced RIHP is not the only cause of the blunted natriuretic response to VE. In a previous study by Patel and Carmines (16), it was suggested that an abnormality in the transduction of changes in RIHP into subsequent natriuresis and diuresis in STZ-diabetic rats might occur. The data in the present study suggest that, although delayed insulin treatment normalizes RIHP response to VE, it may not completely restore the impaired transduction of change in RIHP into natriuresis in response to VE in diabetic rats. Delayed insulin treatment (DDI group) restored RIHP response and partially restored $F_{ENa}$ response to VE in diabetic rats (Figs. 1 and 2). These results suggest attenuation in the relationship between RIHP and $F_{ENa}$ in response to VE in DDI group of rats with delayed insulin treatment compared with normalization of this relationship in diabetic rats with early insulin treatment (DI group). Further studies are required to fully elucidate the exact mechanism of the attenuated relationship between RIHP and $F_{ENa}$ in response to VE in diabetic rats with delayed insulin treatment. It should be noted that the blunted natriuretic response to VE in STZ-diabetic rats is markedly improved (16) or corrected (17) by renal denervation and is corrected by the restoration of blood glucose levels to normal by chronic insulin treatment (15, 18).

Based on human and animal studies, it appears that the blunted natriuretic response to VE in diabetes may be partially mediated by hemodynamic and/or hormonal changes such as changes in atrial natriuretic peptide and the renin-angiotensin system (15, 18).

In the present study clearances of both lithium and phosphate were utilized as indexes of proximal tubule reabsorption (1, 21). Fractional excretion of lithium ($F_{ELi}$) and fractional excretion of phosphate ($F_{EPi}$) were determined during control and VE periods to evaluate possible changes in proximal tubular reabsorption in all groups of rats studied. In the present study, the significantly attenuated $F_{ELi}$ and $F_{EPi}$ responses to VE in untreated diabetic (Table 2 and Fig. 3) compared with control rats suggest that there is increased proximal tubular reabsorption with VE in the diabetic state. These attenuated $F_{ELi}$ and $F_{EPi}$ in untreated diabetic compared with control rats are associated with a blunted increase in RIHP ($\Delta RIHP$) in response to VE (Table 2 and Figs. 1–3), suggesting a proportional positive correlation between increases in RIHP and decreases in proximal tubular reabsorption, as well as natriuresis and diuresis in response to VE. Insulin treatment initiated immediately after the onset of diabetes (DI group) restored the $F_{ELi}$ and $F_{EPi}$ responses to VE, suggesting normalization of the proximal tubular response to VE in these rats. In the DI group of rats, $\Delta RIHP$, $\Delta F_{ENa}$, $\Delta V$, $\Delta F_{ELi}$, and $\Delta F_{EPi}$ were all similar to those that are observed in control rats (C group) with VE.

**Fig. 3.** Changes in fractional excretion of lithium ($\Delta F_{ELi}$) and fractional excretion of phosphate ($\Delta F_{EPi}$) in response to VE in normal control, untreated diabetic, diabetic + immediate insulin treatment, and diabetic + delayed insulin treatment groups of female Sprague-Dawley rats. *Significant difference compared with untreated diabetic group of rats using a 1-way ANOVA, followed by a post hoc Bonferroni correction. ‡Significant difference compared with normal control group of rats using a 1-way ANOVA, followed by a post hoc Bonferroni correction.
(Figs. 1–3), suggesting that insulin treatment initiated immediately after the onset of diabetes restores the renal response to VE to normal levels. Delayed insulin treatment initiated 2 wk after STZ injection (DII group) restored ΔRIHP but not ΔFENa, ΔFELi, or ΔFECr responses to VE (Figs. 1–3). It appears that delayed insulin treatment resulted in a blunting of the proportional positive correlation between increases in RIHP, decreases in proximal tubular reabsorption, and natriuresis in response to VE that occur in control rats (C) and in diabetic rats with immediate insulin treatment (D1).

DM is a complex disease that involves multisystem disturbances including carbohydrate and lipid metabolism, as well as altered fluid balance and an increase in exchangeable sodium (15). It has been proposed that the regulation of sodium and fluid balance in the early stages of diabetes may have a significant impact on the long-term cardiovascular and renal complications of the diabetic state (15). Sodium retention occurs early in diabetes, and it has been suggested that diabetic patients who are unable to compensate for these early changes in sodium handling may develop diabetic nephropathy and/or hypertension, which are complications that can ultimately lead to chronic renal failure (15). These suggestions highlight the importance of understanding the differences between initiating insulin treatment early or later during the course of diabetes, as well as the possible long-term benefits of early treatment. The results of the present study indicate that unlike immediate initiation of insulin treatment, delayed insulin treatment cannot completely restore ΔFENa, ΔFELi, and ΔFECr to VE in diabetic rats, suggesting that delayed insulin treatment may not fully reverse the renal excretory response to VE. These data may support the importance of the notion of initiating insulin treatment as soon as diabetes is confirmed to protect against deteriorations in renal function.

In summary, the present study indicates that, in STZ-induced diabetic rats, basal RIHP and the increase in RIHP during VE are attenuated, resulting in blunted natriuretic and diuretic responses to VE in these rats. Insulin treatment initiated immediately after the onset of diabetes restores basal RIHP and RIHP response to VE, which contributes to the maintenance of normal natriuretic and diuretic responses to VE. However, delayed insulin treatment restores the basal RIHP and RIHP response to VE but does not fully restore the natriuretic response to VE.

GRANTS

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REFERENCES