Moderate Dietary Salt Restriction Increases Vascular and Systemic Insulin Resistance

Ross D. Feldman and Nancy D. Schmidt

Our recent studies have indicated that severe salt restriction aggravates vascular insulin resistance in younger normotensive and hypertensive subjects. However, whether the extent of dietary salt restriction commonly advocated adversely affects vascular insulin resistance is unknown. To determine whether moderate dietary salt restriction might affect vascular and systemic sensitivity to insulin, we studied eight subjects after 1 week of a normal sodium diet (235 mEq/day) and 1 week of a moderate salt restriction (75 meq/day). Systemic insulin resistance as assessed by the fasting plasma glucose-to-insulin ratio was aggravated by dietary sodium restriction (normal sodium: 1.2 ± 0.1 mmol/mIU; low sodium 0.6 ± 0.1, P < .05). Salt restriction significantly reduced maximal insulin-mediated vasodilation (normal sodium: 51% ± 5% of maximum nitroglycerin-mediated response; low sodium: 28% ± 6%, P < .01). In contrast, no alterations in nitroglycerin-mediated vasodilation nor phenylephrine-mediated vasoconstriction were noted. These studies demonstrate that moderate salt restriction aggravates both systemic and vascular insulin resistance. This impairment of the vasodilating effect of insulin could be a factor attenuating the blood pressure lowering effect of a low sodium diet. Am J Hypertens 1999;12:643–647 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Insulin resistance, salt, vasodilation.

Restricting dietary sodium chloride intake has an important role in the treatment of hypertension. Sodium restriction is effective in lowering blood pressure, especially in older patients. However, the effectiveness of dietary sodium restriction in lowering blood pressure in younger patients may be more modest. Additionally, the implications of advocating dietary salt restriction on a public health basis remain controversial. It has been appreciated that dietary sodium restriction may be associated with metabolic and neural effects that might attenuate its blood pressure lowering response as well as adversely modify a patient’s overall risk for atherosclerotic disease. Severe dietary sodium restriction may result in elevated sympathetic nerve activity and has been associated with adverse effects on serum lipid and glucose metabolism.

Insulin resistance is a risk factor for hypertension, although the causality of the relationship has not been proved. However, besides its effects on glucose metabolism, insulin has been demonstrated to be a vasodilator. Furthermore, resistance to the vasodilating effects of insulin occurs in hypertension and might be linked to the elevation of peripheral resistance that is the hallmark of the disease. Severe dietary

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sodium restriction has been shown to increase resistance to the systemic effects of insulin, although these findings have not been universal. Studies from our laboratory have demonstrated that sodium restriction increases vascular insulin resistance in both normotensive and hypertensive subjects. However, in those studies, vascular sensitivity to insulin was assessed after severe sodium restriction (20 mEq/day)—far in excess of the degree of sodium restriction attainable clinically. Whether vascular insulin resistance occurs with a more moderate sodium restriction (more similar to that used clinically in nonpharmacologic therapy of hypertension and in prevention of hypertension) was unknown. Relative to these uncertainties, we have studied the effects of moderate dietary sodium restriction (75 mEq/day) on vascular and systemic insulin resistance in subjects with normal and high normal/borderline blood pressure. The data presented demonstrates that more moderate sodium restriction still reduces both vascular and systemic insulin sensitivity.

**METHODS**

**Study Design**  The effect of moderate dietary sodium restriction on insulin sensitivity was studied in eight male subjects using a randomized, crossover, double blind design. Subjects were 25 to 40 years of age. Subjects had no abnormalities on history and physical examination and no subject smoked tobacco products. Subjects demonstrated a range of blood pressure from normotensive to high normal/borderline. High normal/borderline subjects demonstrated intermittently normal clinic blood pressures but 20% of their daytime automatic ambulatory blood pressure readings were >140 mm Hg systolic or 90 mm Hg diastolic. Subjects did not take any medications on a regular basis and refrained from taking any medication for at least 1 week before the study. Subjects had no laboratory evidence of impaired glucose tolerance. Immediately before the study, a 24-h ambulatory automatic ambulatory blood pressure recording (SpaceLabs, Redmond, WA) was performed. Subjects were given a standardized diet that contained 75 mmol/L sodium chloride, 60 mmol/L potassium, and 20 mmol/L calcium for 14 days. Diets contained 16% protein, 54% carbohydrate, and 35% fat. Caloric intake was 2800 kcal/day. Subjects were advised to drink approximately 2 L of water/day. To assess the effects of dietary salt restriction independent of other dietary changes, subjects were randomized on a double blind cross-over basis to a daily supplement of 16 tablets of slow release sodium (Novartis, Mississauga, Ontario; 10 mmol/L sodium chloride/tablet) or matching placebo. Each were administered for 7 days. The effect of dietary salt intake on blood pressure was assessed by 24-h automatic ambulatory blood pressure monitoring on the study days 6 and 13. A 24-h urine collection for sodium over the last day of each diet was used as a measure of dietary compliance. On the mornings of study days 6 and 13, and ≥20 min after an intravenous catheter insertion and supine rest, a fasting blood sample was collected for determination of catecholamines, glycated hemoglobin, glucose, and insulin. Vascular sensitivity to insulin was assessed by the dorsal hand vein linear variable differential transformer (LVDT) technique.

**Assessment of Vascular Sensitivity to Insulin by Dorsal Hand Vein Linear Variable Differential Transformer Technique**  Studies using the LVDT technique in dorsal hand veins were performed according to our previously described methods. Baseline venous distension was assessed after compression of the ipsilateral arm with a sphygmomanometer cuff inflated to 50 mm Hg. The extent of this distension at baseline was defined as 100%. Phenylephrine-mediated vasoconstriction was assessed by infusion of increasing doses from 16 to 20,000 ng/min (in normal saline at an infusion rate of 0.1 mL/min and parallelled by infusion of 2% whole blood in saline at a rate of 0.1 mL/min). In preliminary studies we determined that 2% blood/saline infusion did not alter the extent of submaximal phenylephrine-mediated constriction (data not shown). The maximal extent of phenylephrine-mediated constriction and the potency of phenylephrine (as defined by the dose that produced half-maximal effect [ED50]) was determined by computerized nonlinear curve fitting (Sigmoid Plot, Subroutine, Prism 2.0, GraphPad Software, San Diego, CA). To assess the extent of insulin-mediated attenuation of phenylephrine-mediated vasoconstriction, veins were preconstricted with phenylephrine at a dose that achieved approximately 80% of the maximum phenylephrine-induced effect; the dose was individualized for each subject in each study. In the assessment of vasodilator responses, the extent of venous distension achieved with this dose of phenylephrine was defined as 0% venodilation. Insulin was then concurrently infused at a dose of 30 to 10,000 μU/min in normal saline with 2% whole blood at an infusion rate of 0.1 mL/min. Capillary glucose concentrations from the contralateral arm were measured and blood glucose concentrations were maintained with oral glucose tablets. Maximum insulin-mediated venodilation and ED50 for insulin were determined by analysis of the data by curve fitting techniques, as previously described. Maximal isoproterenol-mediated vasorelaxation was determined in phenylephrine-preconstricted vessels at an isoproterenol dose of 100 ng/min. Maximal nitroglycerin-mediated vasorelaxation was determined at a nitroglycerin dose of 100 ng/min.
Laboratory Analysis  Serum and urine sodium were determined by ion-selective electrode analysis. Serum glucose was measured by the glucose oxidase method. Plasma norepinephrine was determined by high pressure liquid chromatography with electrochemical detection. Glycated hemoglobin was determined by acid-buffered agarose gel electrophoresis. Immunoreactive plasma insulin was determined by radio immunoassay.

RESULTS
Dietary sodium restriction was associated with a significant decrease in 24-h urinary sodium excretion. However, blood pressure (based on the average 24-h automatic ambulatory measurements) was not significantly decreased with dietary salt restriction (Table 1). Moderate salt restriction was associated with a significant increase in plasma norepinephrine concentrations (Table 1). Dietary salt restriction was associated with a significant decrease in the glucose-to-insulin ratio, suggesting increased systemic insulin resistance (Table 1, Figure 1). This decrease was primarily accounted for by an increase in plasma insulin concentration (Table 1).

Dietary salt restriction was associated with a significant reduction in maximal insulin-mediated vasodilation (i.e., attenuation of phenylephrine-mediated vasoconstriction) (Figure 1). No consistent alteration in insulin potency (ED50 insulin) was evident (Table 2). Further, neither isoproterenol nor nitroglycerin-mediated vasodilation were altered with sodium restriction (Table 2). Phenylephrine-mediated constriction was also unaltered with dietary sodium restriction (Table 2). The extent of impairment of insulin-mediated vasodilation with salt restriction was not correlated with baseline mean arterial pressure (i.e., comparable across the

### TABLE 1. EFFECTS OF DIETARY SALT RESTRICTION ON HEMODYNAMIC AND METABOLIC PARAMETERS

<table>
<thead>
<tr>
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<th>Normal Salt</th>
<th>Low Salt</th>
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<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>99 ± 3</td>
<td>99 ± 3</td>
</tr>
<tr>
<td>Plasma norepinephrine (pmol/L)</td>
<td>839 ± 112</td>
<td>1153 ± 171*</td>
</tr>
<tr>
<td>Plasma glycated Hb (%)</td>
<td>4.9 ± 0.1</td>
<td>4.7 ± 0.2</td>
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<tr>
<td>Plasma cholesterol (mmol/L)</td>
<td>4.8 ± 0.2</td>
<td>5.0 ± 0.2</td>
</tr>
<tr>
<td>Urinary sodium excretion (mEq/day)</td>
<td>207 ± 17</td>
<td>48 ± 6*</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>4.8 ± 0.2</td>
<td>5.0 ± 0.3</td>
</tr>
<tr>
<td>Plasma insulin (mIU/L)</td>
<td>4.4 ± 0.6</td>
<td>9.9 ± 2.0*</td>
</tr>
<tr>
<td>Glucose/insulin ratio (mmol/mIU) (mmol/L/mIU/L)</td>
<td>1.2 ± 0.1</td>
<td>0.6 ± 0.1*</td>
</tr>
</tbody>
</table>

Data represent the mean ± SEM.
*P < .05 v normal salt.

### TABLE 2. EFFECTS OF DIETARY SALT RESTRICTION ON VASCULAR REACTIVITY: LINEAR VARIABLE DIFFERENTIAL TRANSFORMER (LVDT) STUDIES

<table>
<thead>
<tr>
<th></th>
<th>Normal Salt</th>
<th>Low Salt</th>
</tr>
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<tbody>
<tr>
<td>Log ED50 insulin (log μU/min)</td>
<td>2.48 ± 0.41</td>
<td>2.11 ± 0.22</td>
</tr>
<tr>
<td>Maximal insulin-mediated dilation (% NTG)</td>
<td>51 ± 5</td>
<td>28 ± 6*</td>
</tr>
<tr>
<td>Maximal isoproterenol-mediated vasodilation (% NTG)</td>
<td>66 ± 10</td>
<td>70 ± 7</td>
</tr>
<tr>
<td>Maximal nitroglycerin-mediated vasodilation (% baseline)</td>
<td>105 ± 9</td>
<td>102 ± 3</td>
</tr>
<tr>
<td>Log ED50 phenylephrine (log ng/min)</td>
<td>2.25 ± 0.14</td>
<td>2.33 ± 0.21</td>
</tr>
<tr>
<td>Baseline distension (mm)</td>
<td>1.05 ± 0.15</td>
<td>0.91 ± 0.06</td>
</tr>
<tr>
<td>Distension at 80% maximal vasoconstriction (mm)</td>
<td>0.47 ± 0.10</td>
<td>0.33 ± 0.04</td>
</tr>
</tbody>
</table>

Data represent the mean ± SEM.
* P < .05 v normal salt diet.
DISCUSSION

Previous studies from our laboratory and those of others have shown that insulin is a direct vasodilator,11–14 that insulin-mediated vasodilation is impaired in hypertension and obesity,12,15,16 and that insulin-mediated vasodilation is regulatable.16 We have demonstrated previously that in normotensive subjects vascular insulin sensitivity is impaired by severe sodium restriction.16 Furthermore, in hypertensive subjects severe salt restriction exacerbates the pre-existing impairment in vascular sensitivity to insulin. The present studies indicate that in subjects with normal and high normal blood pressure, moderate dietary sodium restriction (to the extent commonly prescribed in the treatment of hypertension) results in significant impairment in maximal insulin-mediated vasodilation. This impairment in the vasodilating effects of insulin parallels a reduction in systemic insulin sensitivity.

Impaired response to the systemic effects of insulin have been previously demonstrated with severe sodium restrictions (generally in the range of 20 to 30 mEq/day).8,9,17–19 Current studies indicate that moderate salt restriction in younger subjects results in comparable impairment in systemic insulin resistance—at least as assessed by fasting glucose-to-insulin ratios. It should be noted that more sensitive methods for assessing alterations in systemic insulin sensitivity would include determination of glucose uptake after hyperinsulinemic clamping or by using frequently sampled intravenous glucose tolerance tests, as we have used previously.22 However, a major limitation of the use of fasting glucose and insulin concentrations appears to be their sensitivity as an index of insulin resistance.23–25 Thus, our ability to detect a significant alteration in the plasma glucose-to-insulin ratio and an alteration in fasting plasma insulin concentrations alone (which may provide a comparable index of insulin resistance and may be more predictive as a coronary heart disease risk factor)26 would argue that moderate salt restriction was associated with a true increase in systemic insulin resistance. It is notable that in a study of eight older obese, sedentary hypertensive subjects, no alterations in systemic insulin resistance were apparent after a milder degree of sodium restriction (3 g sodium, 130 mEq/day).27 Why our findings differ is unclear, but could reflect differences in the study population or relate to a threshold effect of the extent of dietary salt restriction on systemic insulin resistance.

The increase in systemic insulin resistance seen with dietary salt restriction parallels an increase in vascular insulin resistance. This effect was selective for insulin-mediated vasodilation and not reflected in alterations to either isoproterenol (β-adrenergic) or nitroglycerin-mediated vasodilation. Insulin mediates its vascular effects by an endothelium-dependent mechanism via generation of nitric oxide,28,29 and consequent activation of vascular smooth muscle guanylate cyclase. This effect on guanylate cyclase activation is mimicked by nitroglycerin. Thus, the effect of dietary sodium restriction to impair insulin- but not nitroglycerin-mediated vasodilation would suggest that the mechanism was either insulin receptor-specific or specific for endothelial vasodilator mechanisms.

Although maximal insulin-mediated vasodilation was impaired, no significant alterations in the potency of insulin (ED$_{50}$) were seen. Our previous studies assessing alterations in vascular sensitivity to insulin have generally identified regulation of insulin potency but not maximal insulin-mediated responses. Indeed, in our previous study of the effects of severe sodium restriction on vascular sensitivity to insulin, the primary alteration seen was an increase in ED$_{50}$. The explanation for the previous finding of impaired potency and the present finding of impaired maximal effect is unclear but probably reflects differences in techniques of insulin infusion. In our prior studies12,16,22 we infused insulin mixed in 5% dextrose. In the present studies we infused insulin in whole blood. The former approach results in significant trappings of insulin on plastic, especially at lower insulin concentrations and, hence, a significant systematic overestimation of the ED$_{50}$ for insulin (RD Feldman, ND Schmidt, unpublished observations). In the present studies using whole blood, we have seen a significant reduction in the average ED$_{50}$ for insulin (as compared with our initial studies). Indeed the maximal concentration of insulin used in the present studies is less than one tenth of the maximal dose used in our prior studies, and more closely approximates the ED$_{50}$ concentration used previously.

In summary, our studies have shown that in younger subjects, moderate dietary salt restriction may have adverse effects on both vascular and systemic sensitivity to insulin. Significant questions remain. The relative importance of insulin-mediated vasodilation in the maintenance of peripheral vascular resistance has yet to be established. Furthermore, whether the net vascular effect of insulin is impaired (ie, reflecting some product of insulin sensitivity and plasma insulin concentration) remains unknown. However despite these uncertainties, our studies do raise the hypothesis that an impairment in the effects of insulin-mediated responses could contribute to the relative ineffectiveness of dietary salt restriction in reducing blood pressure in younger subjects.
REFERENCES


