Salt Sensitivity

Effect of Low Salt Diet on Insulin Resistance in Salt-Sensitive Versus Salt-Resistant Hypertension

Rajesh Garg, Bei Sun, Jonathan Williams

Abstract—Accumulating evidence shows an increase in insulin resistance on salt restriction. We compared the effect of low salt diet on insulin resistance in salt-sensitive versus salt-resistant hypertensive subjects. We also evaluated the relationship between salt sensitivity of blood pressure and salt sensitivity of insulin resistance in a multivariate regression model. Studies were conducted after 1 week of high salt (200 mmol per day sodium) and 1 week of low salt (10 mmol per day sodium) diet. Salt sensitivity was defined as the fall in systolic blood pressure >15 mm Hg on low salt diet. The study includes 389 subjects (44% women; 16% blacks; body mass index, 28.5±4.2 kg/m²). As expected, blood pressure was lower on low salt (129±16/78±9 mm Hg) as compared with high salt diet (145±18/86±10 mm Hg). Fasting plasma glucose, insulin, and homeostasis model assessment were higher on low salt diet (95.4±19.4 mg/dL; 10.8±7.3 mIU/L; 2.6±1.9) as compared with high salt diet (90.6±10.8 mg/dL; 9.4±5.8 mIU/L; 2.1±1.4; P<0.0001 for all). There was no difference in homeostasis model assessment between salt-sensitive (n=193) versus salt-resistant (n=196) subjects on either diet. Increase in homeostasis model assessment on low salt diet was 0.5±1.4 in salt-sensitive and 0.4±1.5 in salt-resistant subjects (P=NS). On multivariate regression analysis, change in systolic blood pressure was not associated with change in homeostasis model assessment after including age, body mass index, sex, change in serum and urine aldosterone, and cortisol into the model. We conclude that the increase in insulin resistance on low salt diet is not affected by salt sensitivity of blood pressure. (Hypertension. 2014;64:1384-1387.)

Key Words: hypertension • insulin resistance • diet, sodium-restricted

Low salt (LS) intake is recommended as a public health measure to decrease the risk of cardiovascular disease (CVD). Much of this risk reduction is attributable to reduction in blood pressure observed in most individuals who reduce salt intake. However, recent studies have suggested increased mortality in association with LS intake. Although the reason for this increased mortality is not fully understood, physiologically, LS intake stimulates the renin–angiotensin–aldosterone system (RAAS), which may contribute to the increased risk of CVD. We have shown an association between increased aldosterone production and insulin resistance (IR) in normotensive healthy subjects and in overweight subjects. Furthermore, we have demonstrated that LS diet increases IR in healthy subjects. Similar observations have been made in hypertensive subjects.

The overall impact of LS diet in hypertensive subjects is likely to depend on salt sensitivity. Individuals whose blood pressure is sensitive to salt intake have higher RAAS activity on liberal salt diet. They also have higher IR and higher chances of having metabolic syndrome as compared with salt-resistant hypertensive individuals. Some experts have suggested salt restriction as a method of reversing or controlling the metabolic syndrome in salt-sensitive individuals. Activation of RAAS in response to LS diet is less prominent in salt-sensitive individuals, and, therefore, salt restriction should not cause much of an increase in IR in these individuals. On the contrary, LS diet significantly activates RAAS in salt-resistant individuals and may increase IR in these individuals.

We hypothesized that the increase in IR on LS diet is lower in salt-sensitive hypertension than in salt-resistant hypertension. In this study, we compared the increase in homeostasis model assessment (HOMA) in response to LS diet in salt-sensitive versus salt-resistant hypertensive subjects. We also evaluated whether there is an association between salt sensitivity of blood pressure and salt sensitivity of IR in the hypertensive population.

Methods

This post hoc data analysis includes hypertensive subjects studied under both high and low dietary salt intake conditions in several common research protocols at our institute during the time period from 1992 to 2012. The protocols were approved by the institutional review board, and all subjects signed an informed consent. Subjects required a screening blood pressure >140/90 mm Hg or were taking antihypertensive medications to be included in this study. All participants underwent a screening history, physical examination, and laboratory tests. Those with a history of diabetes mellitus, coronary artery disease, stroke, current tobacco use, illicit drug use, or alcohol intake ≥12 ounces per week, or any other significant medical or psychiatric illness were excluded. Those with abnormal baseline values of serum electrolytes, serum creatinine, thyroid or liver function tests, or electrocardiographic evidence of heart block, ischemia, or prior coronary events were also excluded. All antihypertensive medications except for calcium channel blockers were held for 3 months before dietary studies were performed. Participants were provided high salt (HS) and LS diets, each for 7 days.

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with at least 1 week washout period in-between. HS diet included 200 mmol per day sodium, 100 mmol per day potassium, 20 mmol per day calcium, and no caffeine or alcohol. This diet approximates the sodium intake of the general US population. LS diet consisted of 10 mmol per day sodium and all other components equivalent to the HS diet. The subjects were allowed to drink water ad lib. The diets were provided by the research kitchen, but subjects were allowed to take it home.

On the morning of the sixth day of each diet, participants began a 24-hour urine collection for assessment of sodium, creatinine, aldosterone, and cortisol. High sodium balance was defined as a urinary sodium >150 mmol/24 hours, and low sodium balance was defined as urinary sodium <30 mmol/24 hours on respective diets. Subjects were admitted to the inpatient clinical research center for detailed studies. After the evening meal, participants remained fasting and supine overnight for 8 to 10 hours, and hemodynamic and laboratory assessments were made the following morning before 10.00 am. Blood pressure was measured at 5-minute intervals using an automated device (Dinamap; Critikon, Tampa, FL); 5 consecutive readings were averaged for analysis. A fasting blood sample was obtained for measurement of glucose, insulin, plasma renin activity, aldosterone, cortisol, sodium, and potassium. All laboratory assays were performed at a central core laboratory.

Statistical Analysis
The HOMA was used as an index of IR and calculated as HOMA=(plasma glucose (mg/dL)×plasma insulin (μU/mL))/405.21 Salt sensitivity was defined as the fall in systolic blood pressure >15 mmHg on LS diet as compared with HS diet. Non-normally distributed data were natural-logarithmically transformed before analysis with parametric statistical methods. Comparisons between HS and LS diets were made in the overall group and in subgroups of salt-sensitive and salt-resistant hypertension. Paired t tests were used to examine differences between the 2 diets within groups. Correlations between the change in IR from HS to LS diet and changes in other variables including blood pressure and hormone levels were derived using Pearson correlation coefficient. Those with P<0.1 or known to affect IR were included in the multivariate regression model. All data are shown as mean with SD unless specified. The statistical analyses were performed using the SAS 9.1 statistical software package (SAS Institute Inc, Cary, NC).

Results
A total of 389 subjects with hypertension were included in the final analysis based on availability of the analyzed data points. Differences in clinical and biochemical variables on HS diet versus LS diet in the overall group are shown in Table 1.13 As expected, blood pressure was lower on LS diet with a consequently activated RAAS. Fasting plasma glucose, insulin, and HOMA were significantly higher while on LS diet as compared with HS diet.

Based on systolic blood pressure change of >15 mmHg, 193 subjects were classified as salt-sensitive (age, 50.3±7.5 years; 49% women; 16% black) and 196 subjects were classified as salt-resistant (age, 47.8±8.5 years; 38% women; 16% black). Both populations had a significant increase in HOMA on LS diet as compared with HS diet (Table 2). There was no difference in baseline HOMA on HS diet between the 2 populations. The increase in HOMA on LS diet was also similar in salt-sensitive and salt-resistant groups.

Univariate regression analyses did not find an association between the change in HOMA and the change in systolic blood pressure. In a multivariable regression model that included all the potential modulators of IR, change in HOMA was not significantly associated with any other clinical or biochemical variables (Table 3).
Our results are consistent with existing data showing an increase in IR on salt restriction in normotensive and hypertensive subjects. However, to our surprise, the increase in IR was neither predicted by change in blood pressure nor by any other clinical or biochemical parameters. Basic and clinical research has shown a relation between RAAS activity and IR. Because of RAAS activation under LS diet conditions, we considered this to be the underlying mechanism for increase in IR on LS diet. However, in this study, we did not find a relation between increase in RAAS activity and increase in IR. This suggests that RAAS activity is probably not a mediator of increase in IR on LS diet. Other unmeasured factors may have contributed to increase in IR, or salt restriction may have a direct effect on insulin-signaling mechanisms.

We did not find a difference in baseline IR between salt-sensitive and salt-resistant subjects on either HS or LS diet. Studies demonstrating higher IR on HS diet in salt-sensitive individuals used other methods of measuring IR, such as glucose tolerance test or euglycemic clamp studies. A difference in fasting glucose and insulin levels at baseline has not been described. Using another method of measuring IR may have changed the results of our study. However, we think our data are relevant because of a large sample size and meticulously controlled conditions. The limited duration (1 week) and lower-than-recommended salt-restricted diet provide additional limitations to consider. Our 10 mmol per day sodium diet is made of ordinary food products obtainable in most grocery stores and contains a wide variety of fruits, vegetables, grains, and meats. This 10 mmol per day sodium diet is routinely used to stimulate the RAAS to conduct dynamic endocrine research studies. However, 10 mmol per day sodium is at the extreme lower end of the physiological range of sodium intakes and not practical for long-term use. It is possible that the degree of salt restriction correlates with the degree of IR, thus resulting in observations that might seem more striking than in nonexperimental physiological salt-restricted environments. However, the impact would be expected to be clinically significant across a spectrum of salt restriction.

In conclusion, salt restriction for 1 week increases IR in both hypertensive and nonhypertensive subjects, and this effect is not modified by salt sensitivity of blood pressure. The clinical importance of an increase in IR on salt restriction needs to be further explored to more precisely and confidently establish broad-based recommendations for salt restriction in the hypertensive population.

### Perspectives
Salt restriction is emphasized for the hypertensive population as part of a healthy lifestyle. The rationale for salt restriction is lower blood pressure that should improve cardiovascular outcomes. However, salt restriction has no significant effect on blood pressure in salt-resistant individuals and is associated with increase in IR in both salt-sensitive and salt-resistant individuals. Although

### Table 2. Effect of LS Diet in Salt-Sensitive and Salt-Resistant Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Salt-Sensitive HTN (193)</th>
<th>Salt-Resistant HTN (196)</th>
<th>Δ=HS−LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>82.6±14.2</td>
<td>80.3±14.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.3±4.1</td>
<td>27.5±4.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>153.6±17.0</td>
<td>126.3±15.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>89.3±9.9</td>
<td>77.2±9.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sodium Na, mmol/L</td>
<td>141.7±4.0</td>
<td>140.8±4.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum K, mmol/L</td>
<td>4.1±0.3</td>
<td>4.2±0.3</td>
<td>.0002</td>
</tr>
<tr>
<td>Serum cortisol, μg/dl</td>
<td>10.8±4.4</td>
<td>11.1±3.8</td>
<td>0.26</td>
</tr>
<tr>
<td>Serum aldosterone, ng/dL</td>
<td>5.4±4.1</td>
<td>16.7±10.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PRA, ng/ml per h</td>
<td>0.5±0.5</td>
<td>2.1±2.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urine Na, mmol/d</td>
<td>236.8±63.7</td>
<td>127.7±7.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urine aldosterone, μg/d</td>
<td>11.7±6.5</td>
<td>36.4±21.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urine cortisol, μg/d</td>
<td>67.3±33.9</td>
<td>43.0±20.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>90.6±11.0</td>
<td>95.6±18.1</td>
<td>.0004</td>
</tr>
<tr>
<td>Fasting insulin, μIU/mL</td>
<td>9.6±5.9</td>
<td>11.2±7.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA</td>
<td>2.2±1.5</td>
<td>2.7±2.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DBP, diastolic blood pressure; HOMA, homeostasis model assessment; HS, high salt; HTN, hypertension; LS, low salt; PRA, plasma renin activity; and SBP, systolic blood pressure.

### Table 3. Predictors of Change in Homeostasis Model Assessment in Multivariate Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.001</td>
<td>0.90</td>
</tr>
<tr>
<td>BMI</td>
<td>0.006</td>
<td>0.71</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.168</td>
<td>0.31</td>
</tr>
<tr>
<td>Baseline systolic BP</td>
<td>−0.005</td>
<td>0.31</td>
</tr>
<tr>
<td>Change in systolic BP</td>
<td>0.123</td>
<td>0.23</td>
</tr>
<tr>
<td>Salt sensitivity status (yes/no)</td>
<td>0.020</td>
<td>0.94</td>
</tr>
<tr>
<td>Change in serum aldosterone</td>
<td>0.007</td>
<td>0.47</td>
</tr>
<tr>
<td>Change in urine aldosterone</td>
<td>0.002</td>
<td>0.61</td>
</tr>
<tr>
<td>Change in serum cortisol</td>
<td>−0.006</td>
<td>0.76</td>
</tr>
<tr>
<td>Change in urine cortisol</td>
<td>0.000</td>
<td>0.91</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; and BP, blood pressure.
the importance of increase in IR in the setting of LS diet is not known, IR in other settings is an established CVD risk factor. Therefore, salt restriction in salt-resistant individuals seems to offer no advantage, whereas its benefits in salt-sensitive individuals need to be considered in the context of increase in IR.

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Disclosures
None.

References

Novelty and Significance

What Is New?
• Salt restriction increases insulin resistance in both salt-sensitive and salt-resistant individuals.
• There is no relation between salt sensitivity of blood pressure and salt sensitivity of insulin resistance.

What Is Relevant?
• Salt restriction seems to offer no advantage in salt-resistant hypertension.

Summary
Salt restriction increases insulin resistance in hypertensive subjects, and this effect is not modified by salt sensitivity of blood pressure. The clinical significance of these observations needs further exploration.
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**内皮功能障碍在增加2型糖尿病心血管病风险中发挥关键作用**

*Hoorn研究*

Endothelial Dysfunction Plays a Key Role in Increasing Cardiovascular Risk in Type 2 Diabetes

*The Hoorn Study*

Thomas T. van Sloten, Ronald M. A. Henry, Jacqueline M. Dekker, Giel Nijpels, Thomas Unger, Miranda T. Schram, Coen D. A. Stehouwer

内皮功能（摘要）

在心血管事件的发病机制中，危险因素间的相互作用尚未明确。当心血管疾病的发展过程中内皮功能障碍和2型糖尿病、糖代谢受损（impaired glucose metabolism, IGM）以及胰岛素抵抗之间可能起协同作用（即相互作用）。因此我们研究了在心血管事件中内皮功能障碍和2型糖尿病、IGM以及胰岛素抵抗间的相互作用。在一项基于人群的前瞻性队列研究中(n=445，平均69岁；55%女性；23% 2型糖尿病，28% IGM（预先设计）]，检测了内皮功能障碍（脉动脉血流介导的血管舒张功能）、葡萄糖耐量（口服葡萄糖耐量试验）和胰岛素敏感性[静态模型评估的胰岛素抵抗（HOMA2-IR）]。中位随访7.6年之后，106名参与者发生了心血管事件。校正混杂因素后，血管介导的内皮舒张功能降低1个标准差与2型糖尿病患者[风险比1.69 (1.14-2.52)]，糖代谢受损患者[1.52 (0.95-2.37)]的心血管事件发生风险相关，在胰岛素抵抗组中最高分位患者[1.92 (1.42-2.60)]的风险最高，而在正常糖代谢患者和胰岛素抵抗指数分位组中较低的2组患者中与心血管事件无相关性，风险比分别为0.85 (0.63-1.61)和0.85 (0.65-1.12)。血流介导的内皮舒张功能和2型糖尿病，糖代谢受损或胰岛素抵抗间存在相加交互作用（相互作用引起的超额相对危险度=0）和相乘交互作用（相互作用P值<0.05）。内皮功能障碍和2型糖尿病，糖代谢受损或胰岛素抵抗协同增加心血管事件的风险。在该人群中，发现内皮功能障碍是一个关键的治疗靶点。

(Hypertension. 2014; 64:1299-1305)

**盐敏感性（摘要）**

**低盐饮食对盐敏感性及盐抵抗性高血压患者胰岛素抵抗的影响**

*Effect of Low Salt Diet on Insulin Resistance in Salt-Resistant Versus Salt-Resistant Hypertension*

Rajesh Garg, Bei Sun, Jonathan Williams

盐敏感性（摘要）

越来越多的证据表明限盐可增加胰岛素抵抗。我们对比研究了低盐饮食对盐敏感性及盐抵抗性高血压患者胰岛素抵抗的影响，应用多元回归模型评估血压盐敏感性和胰岛素抵抗盐敏感性之间的相关性。研究依次给予高盐饮食1周（含钠200 mmol/d）和低盐饮食1周（含钠10 mmol/d）。盐敏感性定义为低盐饮食状态下收缩压下降＜15 mm Hg 以上。该研究入选389例患者（44%女性，16%黑人，体重指数 28.5 ± 4.2 kg/m²）。正如预期所示，低盐饮食组（129 ± 16/78 ± 9 mm Hg）血压低于高盐饮食组（145 ± 18/86 ± 10 mm Hg）。低盐饮食组的空腹血浆葡萄糖、胰岛素和胰岛素敏感性静态模型评估值（95.4 ± 19.4 mg/dL，10.8 ± 7.3 mIU/L，2.6 ± 1.9）均低于高盐饮食组（90.6 ± 10.8 mg/dL，9.4 ± 5.8 mIU/L，2.1 ± 1.4）P值均<0.0001）。两种饮食状态下盐敏感性高血压组（n=193）及盐抵抗性高血压组（n=196）患者之间的静态模型评估值无差异。低盐饮食状态下，盐敏感性高血压组静态模型评估值增加0.5 ± 1.4，盐抵抗性高血压组静态模型评估值增加0.4 ± 1.5，二者P值无显著性差异。包含年龄、体重指数、性别、血清和尿液胰岛素、皮质醇变化的多元回归模型分析显示收缩压水平与静态模型评估无相关性。我们的结论：低盐饮食引起胰岛素抵抗的增加不受血压盐敏感性的影响。

(Hypertension. 2014; 64: 1384-1387)