Relation of Dietary Salt and Aldosterone to Urinary Protein Excretion in Subjects With Resistant Hypertension

Eduardo Pimenta, Krishna K. Gaddam, Monique N. Pratt-Ubunama, Mari K. Nishizaka, Inmaculada Aban, Suzanne Oparil, David A. Calhoun

Abstract—Experimental data indicate that the cardioenal effects of aldosterone excess are dependent on concomitant high dietary salt intake. Such an interaction of endogenous aldosterone and dietary salt has not been observed previously in humans. We assessed this hypothesis that excess aldosterone and high dietary sodium intake combine to worsen proteinuria in patients with resistant hypertension. Consecutive subjects with resistant hypertension (n=84) were prospectively evaluated by measurement of 24-hour urinary aldosterone (Ualdo), sodium, and protein (Uprot) excretion. Subjects were analyzed according to aldosterone status (high: Ualdo ≥12 μg/24 hours; or normal: <12 μg/24 hours) and dietary salt intake based on tertiles of urinary sodium. The mean clinic blood pressure for all of the subjects was 161.4±22.4/89.8±13.5 mm Hg on an average of 4.3 medications. There was no blood pressure difference between study groups. Uprot was significantly higher in the 38 subjects with high Ualdo compared with the 46 subjects with normal Ualdo (143.0±83.8 versus 95.9±81.7 mg/24 hours; P=0.01). Among subjects with high Ualdo, Uprot increased progressively across urinary sodium groups (P<0.05). In contrast, there was no difference in Uprot across sodium tertiles among subjects with normal Ualdo. A positive correlation between Uprot and urinary sodium (r=0.47; P=0.003) was observed in subjects with high Ualdo but not in subjects with normal Ualdo (r=0.18; P value not significant). These results suggest that aldosterone excess and high dietary salt combine to increase urinary protein excretion. (Hypertension. 2008;51:339-344.)

Key Words: hypertension ■ aldosterone ■ salt ■ proteinuria ■ kidney

Aldosterone excess is being increasingly recognized as a common cause of hypertension, with recent reports indicating a prevalence of primary aldosteronism (PA) of 5% to 10% among general hypertensive patients.1-5 Among patients with resistant hypertension, PA is even more common, with a prevalence of ≈20%.6 Animal models indicate that aldosterone excess, in addition to increasing blood pressure (BP), contributes directly to target-organ (heart, brain, and kidney) deterioration by inducing inflammation and perivascular fibrosis.7-9 These same studies have been consistent in demonstrating that the pressor, proinflammatory, and profibrotic effects of aldosterone are dependent on concomitant high dietary salt intake. That is, the deleterious effects of aldosterone are minimized or even prevented by low dietary salt ingestion. Whether such an interaction between aldosterone and dietary salt occurs in humans is unknown.

Increases in intracapillary pressure, structural damage of the glomerular membrane, and impaired endothelial function likely contribute to the development of albuminuria and proteinuria in hypertensive patients.10 Proteinuria is an early sign of nephropathy associated with progressive glomerulosclerosis, tubulointerstitial inflammation, and scarring, with progressive renal function loss in both diabetic and nondiabetic subjects.11 Proteinuria is also independently associated with increases in cardiovascular risk.12-15

The present study was designed to evaluate the effects of endogenous aldosterone and dietary salt, separately and in combination, on proteinuria in subjects with resistant hypertension. In enrolling subjects with resistant hypertension, we were purposefully selecting a cohort known to be at high risk for hyperaldosteronism.

Methods

Subjects
Consecutive subjects referred to the University of Alabama at Birmingham Hypertension Clinic for resistant hypertension were prospectively evaluated. The protocol was approved by the University of Alabama at Birmingham Institutional Review Board for Human Use, and all of the subjects provided written informed consent before study participation. Resistant hypertension was defined as uncontrolled hypertension (>140/90 mm Hg) determined at ≥2 clinic visits despite the use of ≥3 antihypertensive medications at pharmacoologically effective doses. All of the subjects were on a stable antihypertensive regimen for ≥4 weeks before biochemical evaluation. No medications were discontinued before evaluation except for spironolactone, triamterene, or amiloride, which were discontinued for ≥6 weeks before evaluation.

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Subjects were divided into 2 groups according to Ualdo (normal: <12 μg/24 hours; or high: ≥12 μg/24 hours) and into 3 groups according to tertiles of UNa. The cutoff value of Ualdo ≥12 μg/24 hours was chosen to separate the high- and normal-aldosterone groups consistent with current recommendations for diagnosing aldosteronism.18,19 We performed regression analysis separately for normal and high Ualdo groups. A value of P<0.05 for slope of the regression line was considered significant.

Laboratory Assessment

Biochemical evaluation was done in all of the subjects on an outpatient basis. An early morning plasma aldosterone concentration (PAC): plasma renin activity (PRA) ratio (ARR), serum potassium, and creatinine were determined in ambulatory patients after sitting for 5 minutes. A 24-hour urinary collection for aldosterone (Ualdo), sodium (UNa), protein (Uprot), and creatinine was obtained during the subject’s routine diet.

Statistical Analysis

Subjects within the high-Ualdo group had significantly higher PAC, ARR, and CrCl levels. PRA, UNa, and systolic and diastolic BP did not differ between groups. Uprot was significantly higher in high-Ualdo compared with normal-Ualdo subjects (Figure 1).

Results

A total of 84 subjects were evaluated. Thirty-eight of the subjects had high Ualdo and 46 had normal Ualdo (Table). Overall, subjects were on an average of 4.3±1.1 medications, with a mean office BP of 161.4±22.4/89.8±13.5 mm Hg. Both the numbers and types of antihypertensive medications used were the same in each of the Ualdo-UNa groups. Patients within the high-Ualdo group had significantly higher PAC, ARR, and CrCl levels. PRA, UNa, and systolic and diastolic BP did not differ between groups. Uprot was significantly higher in high-Ualdo compared with normal-Ualdo subjects (Figure 1).

Ualdo, PRA, and office systolic and diastolic BPs were similar across sodium groups in both the high- and normal-Ualdo subjects. Within the high-Ualdo group, Uprot was significantly higher in the third compared with the first tertile of UNa (Figure 2). In contrast, within the normal-Ualdo group, Uprot tended to increase across tertiles of UNa, but differences were not significant. A positive and strong correlation (r=0.468; P=0.003) between the Uprot and UNa was present in high-Ualdo subjects but not in normal-Ualdo subjects (r=0.183; P=0.223; Figure 3, top). CrCl was sig-

**Table. Demographic and Biochemical Values for All of the Subjects and for Subjects Divided by High and Normal Ualdo**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Subjects (n=84)</th>
<th>High Ualdo (n=38)</th>
<th>Normal Ualdo (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, %</td>
<td>46.4</td>
<td>63.2</td>
<td>32.6</td>
</tr>
<tr>
<td>African Americans, %</td>
<td>41.6</td>
<td>39.5</td>
<td>43.4</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.1±10.5</td>
<td>54.9±10.2</td>
<td>55.3±10.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.7±7.1</td>
<td>34.1±7.9</td>
<td>33.4±6.4</td>
</tr>
<tr>
<td>Duration of HTN, y</td>
<td>15.2±9.9</td>
<td>15.3±8.6</td>
<td>15.2±11.0</td>
</tr>
<tr>
<td>No. of medicines</td>
<td>4.3±1.1</td>
<td>4.4±1.2</td>
<td>4.3±1.0</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.0±0.4</td>
<td>4.0±0.5</td>
<td>4.0±0.3</td>
</tr>
<tr>
<td>PAC, ng/dL</td>
<td>11.1±7.6</td>
<td>14.4±9.0</td>
<td>8.3±4.8‡</td>
</tr>
<tr>
<td>PRA, ng/mL/h</td>
<td>3.4±6.5</td>
<td>2.2±3.5</td>
<td>4.4±8.1</td>
</tr>
<tr>
<td>ARR</td>
<td>14.1±17.1</td>
<td>15.7±13.6</td>
<td>8.3±8.7*</td>
</tr>
<tr>
<td>UNa, mEq/24 h</td>
<td>172.3±74.8</td>
<td>177.3±70.2</td>
<td>168.2±78.8</td>
</tr>
<tr>
<td>CrCl, mL/min</td>
<td>105.8±34.7</td>
<td>123.4±32.6</td>
<td>100.0±26.8†</td>
</tr>
<tr>
<td>Uprot, mg/24 h</td>
<td>119.9±87.7</td>
<td>143.0±83.8</td>
<td>95.9±81.7*</td>
</tr>
<tr>
<td>Office BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>161.4±22.4</td>
<td>160.2±22.5</td>
<td>159.4±22.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>89.8±13.5</td>
<td>92.1±14.0</td>
<td>87.1±13.6</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HTN, hypertension; ARR, PAC/PRA ratio. *P<0.05 compared to high-Ualdo. †P<0.001 compared to high-Ualdo. ‡P<0.0001 compared to high-Ualdo.

The office BP was measured after having the subject sit for ≥5 minutes with a mercury sphygmomanometer according to American Heart Association guidelines.16 Secondary causes of hypertension other than hyperaldosteronism, such as renovascular hypertension, pheochromocytoma, or Cushing’s syndrome, were excluded by laboratory analysis and/or radiological imaging as clinically indicated. Subjects with a history of atherosclerotic disease (myocardial infarction or stroke ≤6 months), congestive heart failure, current smoking, diabetes on insulin treatment, or urine protein excretion >300 mg/24 hours were excluded from study participation.

Figure 2. Twenty-four–hour urinary sodium excretion in subjects with high and normal Ualdo according to tertile of urinary sodium excretion. Data are presented as mean±SE. Tertiles of UNa in the high-Ualdo group were defined as <148, 148 to 186, and >186 mEq/24 hours, respectively. Tertiles of UNa in the normal-Ualdo group were defined as <125, 125 to 198, and >198 mEq/24 hours, respectively.
significantly correlated with Uprot in high-Ualdo ($r=0.414$; $P=0.012$) and normal-Ualdo ($r=0.302$; $P=0.043$) subjects (Figure 3, middle). CrCl was significantly correlated with UNa ($r=0.529$; $P=0.001$) in high-Ualdo but not in normal-Ualdo subjects ($r=0.245$; $P=0.105$; Figure 3, bottom).

**Discussion**

The current results demonstrate that, in patients with resistant hypertension and hyperaldosteronism, increasing dietary salt ingestion is associated with progressive worsening of proteinuria. Previous studies in humans have indicated that hyperaldosteronism and high dietary salt independently contribute to increased proteinuria. Previous human studies have demonstrated that aldosterone excess and increasing dietary salt ingestion separately contribute to the development of proteinuria. In a large cross-sectional analysis of 2700 participants, Framingham investigators showed that high dietary salt intake was significantly related to urinary albumin excretion. Albuminuria was 2-fold higher in the highest quintile of urinary sodium excretion compared with the lowest. In this cohort, the highest quintile of serum aldosterone levels was associated with a 21% higher level of urinary albumin excretion compared with the lowest quintile. In this analysis of largely normotensive subjects, the investigators did not find that high plasma aldosterone levels combined with high urinary sodium excretion to worsen albuminuria. The Framingham results are consistent with other studies linking increasing dietary salt ingestion to increases in urinary albumin/protein excretion.

Several observational studies have shown that subjects with PA have higher levels of urinary protein excretion compared with subjects with primary hypertension. The Primary Aldosteronism Prevalence in Hypertensives Study prospectively determined urinary albumin excretion in 490 hypertensive subjects, 64 of whom were confirmed to have PA. Subjects with PA, regardless of whether secondary to an
The pathological processes by which aldosterone and high dietary salt promote proteinuria are undoubtedly multifactorial. First, aldosterone excess through sodium and fluid retention increases BP, which, in turn, would contribute directly to target-organ damage, including the development of proteinuria. Second, aldosterone has known effects on renal hemodynamics that would promote the development of proteinuria. Specifically, aldosterone exerts a direct vasoconstrictive effect on the efferent renal arteriole and/or abolishes potassium chloride–induced vasoconstriction of the afferent arteriole. Such effects would combine to increase renal vascular resistance and glomerular capillary pressure, thereby promoting protein excretion. Lastly, animal models of hyperaldosteronism have clearly established a direct proinflammatory and profibrotic effect of aldosterone and high dietary salt on target-organ tissues.

Consistent with the current results, previous clinical studies suggest that aldosterone excess also promotes urinary protein excretion through the production of a hyperfiltration state. Sechi et al prospectively compared the renal function of 50 subjects with PA to subjects with primary hypertension matched for age, gender, body mass index, and estimated duration of hypertension. PA patients were followed for 6.4 years after treatment with adrenalectomy or aldosterone blockade. All of the classes of antihypertensive medications were allowed in primary hypertensive subjects to reach a goal of 140/90 mm Hg. In spite of similar BP reductions, the decreases in glomerular filtration rate and albuminuria were significantly greater in the PA group. These findings suggest that aldosterone-induced proteinuria in humans is related, at least in part, to intravascular volume retention and subsequent increases in glomerular filtration rate. Such salt sensitivity may be related to the intermediate hypertensive phenotype of “nonmodulators,” described by Hollenberg and Williams, in whom high dietary salt intake does not suppress angiotensin II stimulation of renin and aldosterone release, resulting in an inappropriate increase in sodium and fluid retention.

We and others have demonstrated that PA is a common cause of resistant hypertension, with a prevalence of about 20%. Accordingly, patients with resistant hypertension represent a cohort enriched for hyperaldosteronism and thereby provide a unique opportunity to study causes and/or complications of aldosterone excess in subjects with a history of poorly controlled BP. In this setting, we demonstrate that dietary salt intake likely modulates aldosterone-related proteinuria. Both increased aldosterone levels and increased urinary sodium excretion were associated with higher rates of urinary protein excretion. However, the deleterious effects of high dietary salt were most pronounced in the patients with the highest aldosterone levels, suggesting that excess aldosterone and excess salt intake combine to accelerate renal impairment.

In contrast to the current results, the Framingham investigators did not observe an interaction between high aldosterone levels and high urinary sodium excretion. Important methodologic differences between the Framingham Study and the current study may be relevant to the divergent results. The Framingham Study cohort included a preponderance of normotensive persons in whom PA was presumably uncommon; aldosterone status was based on plasma sampling, and urinary sodium excretion was based on a spot urine collection. In the current analysis, the cohort consisted of subjects with resistant hypertension in whom aldosterone excess is common; aldosterone status was based on 24-hour urinary excretion, which provides a more integrated assessment of plasma secretion than plasma levels, and, lastly, urinary sodium excretion was based on a 24-hour collection.

Because the current study is observational, causality of the higher urinary protein excretion in the high aldosterone-high dietary salt group is not confirmed. However, urinary protein excretion and CrCl were significantly higher in the high compared with the normal aldosterone subjects, and both parameters increased in the high aldosterone subjects with increasing dietary salt intake. This suggests that aldosterone-induced intravascular fluid expansion and consequent increases in glomerular filtration rate (ie, hyperfiltration) may have contributed to the increased proteinuria. Such an effect is supported by studies reporting the antiproteinuric benefit of aldosterone blockade in association with significant reductions in the glomerular filtration rate.

The present study is strengthened by its prospective design and measurement of aldosterone, proteinuria, and sodium excretion by 24-hour urine collection. Study limitations include a cross-sectional design and having evaluated patients during ongoing antihypertensive treatment. Although biochemical evaluation is best done after the withdrawal of antihypertensive medications, this was not possible for safety reasons in these high-risk subjects. All of the subjects were on a stable antihypertensive regimen for ≥4 weeks, such that their sodium balance should have been in steady state. Although antihypertensive medications predictably affect renin activity (β-blockers suppressing and diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers increasing), medication effects on aldosterone excretion are likely less pronounced, tending to have no effect on or to minimally reduce aldosterone secretion. Furthermore, because the medication use in the high- and normal-aldosterone groups was the same, medication-related effects on urinary protein excretion should have been similar.
The current study is also limited by the lack of 24-hour BP measurements. Studies using direct measurements of BP in animals or 24-hour ambulatory BP in humans have shown that elevated systemic BP is a dominant factor in mediating the effects of mineralocorticoid excess on renal function. We have reported recently that ambulatory BP monitoring levels are higher in resistant hypertensive subjects with high compared with normal aldosterone levels in spite of similar office BPs. Such higher 24-hour BPs would be expected to contribute importantly to the increased proteinuria in the high-aldosterone subjects.

**Perspectives**

Animal studies indicate that aldosterone excess and high dietary salt intake in combination have the most pronounced effects on target-organ deterioration. The current study suggests that a similar interaction may be contributing importantly to proteinuria in humans with resistant hypertension. If confirmed, our findings support the testing of treatment strategies based on dietary salt restriction and the use of mineralocorticoid receptor antagonists to help preserve kidney function in subjects with resistant hypertension.

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**Disclosures**

None.

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