Modest Salt Reduction Reduces Blood Pressure and Urine Protein Excretion in Black Hypertensives
A Randomized Control Trial

Pauline A. Swift, Nirmala D. Markandu, Giuseppe A. Sagnella, Feng J. He, Graham A. MacGregor

Abstract—High blood pressure and proteinuria are the major risk factors for cardiovascular and renal disease. In black individuals, there is an increased risk of hypertension, stroke, heart failure, and kidney disease. There are no controlled studies of the effects of reducing salt intake on blood pressure and urine protein excretion in black individuals. Therefore, the aim of our study was to determine the effects of modest salt restriction on blood pressure and urine protein excretion in nondiabetic black hypertensive subjects. The study was randomized, double blind, and placebo controlled. After run-in periods on their usual diet and on reduced salt, participants continued to restrict their salt intake and then received either slow sodium tablets, designed to bring their salt intake back to normal, or placebo tablets for 4 weeks in a randomized, double-blind, crossover study. In the 40 who completed the study, urinary sodium excretion fell on slow sodium to placebo from 169±73 to 89±52 mmol per 24 hours (P<0.001; ≈10 to 5 g salt per day). Blood pressure fell from 159/101±13/8 to 151/98±13/8 mm Hg (P<0.01). Protein excretion fell from 93±48 mg to 75±30 mg per 24 hours (P<0.008). Thus, reducing salt intake from ≈10 to 5 g per day reduced blood pressure and urine protein excretion in black hypertensives. In light of these findings, we would recommend that all black individuals with raised blood pressure reduce their salt intake to ≤5 g per day. (Hypertension. 2005;46:308-312.)

Key Words: blacks • sodium, dietary • blood pressure • proteinuria

Raised blood pressure (BP) occurs more commonly in black individuals, leading to an increased risk of cardiovascular events, particularly stroke.1,2 High blood pressure is also now the second leading cause of end-stage renal disease, with hypertension-related renal disease occurring 4 to 6× more commonly in blacks than in whites.3–5

Raised blood pressure is the major risk factor for cardiovascular morbidity and mortality, whereas blood pressure reduction reduces mortality from stroke, coronary heart disease, and heart failure.6–7 More recently, proteinuria and albuminuria have been implicated as independent risk factors for cardiovascular mortality in hypertensives, diabetics, and the elderly.8–11

In renal disease, high blood pressure and urine protein excretion are major, modifiable risk factors for disease progression.12,13 Outcome trials demonstrate the benefits of reducing blood pressure and urine protein excretion in diabetic and nondiabetic nephropathies.14–17

Salt intake is a major cause of raised blood pressure and a risk factor for renal damage. In clinical and experimental studies, high salt intake is associated independently with hypertension, left ventricular hypertrophy, albuminuria, renal hypertrophy, and fibrosis.18–20 In addition, observational studies demonstrate a positive relationship between salt intake, urine protein excretion, and progression of renal disease.21

Salt reduction reduces blood pressure.22,23 From the few studies that have included black individuals, there is some evidence that black individuals have a greater blood pressure response to salt reduction than their white counterparts.23–25 The Dietary Approaches to Stop Hypertension (DASH)—sodium study (randomized but not double blind) of 3 salt intakes (8, 6, and 4 g per day) showed that the fall in blood pressure tended to be greatest in the black group.26

There are no double-blind, placebo-controlled studies of salt reduction on blood pressure in black individuals; neither are there controlled studies of salt reduction on urine protein excretion. Therefore, the aim of our study was to carry out the first randomized, double-blind, placebo-controlled trial of salt reduction (to the current World Health Organization [WHO]–recommended level of 5 g per day27) in black hypertensives. The primary aim was to determine the effect of salt reduction on blood pressure, and the secondary aim was to determine the effect on urine protein excretion.

Methods

Patients
Black hypertensives (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mm Hg) of African or African–Caribbean origin were
invited to participate in the study. Participants had not been treated with pharmacological antihypertensive agents in the preceding 4 weeks or diuretics in the preceding 8 weeks. Exclusion criteria included severe hypertension (systolic BP ≥200 mm Hg or diastolic BP ≥110 mm Hg), evidence of secondary hypertension, previous stroke, ischemic heart disease, cardiac failure, diabetes mellitus, pregnancy, liver disease, significant renal insufficiency (creatinine ≥1.60 mmol/L), or overt proteinuria (>300 mg of urinary protein per 24 hours). The local research ethics committee (LREC) approved the study, and all procedures followed were in accordance with LREC guidelines. Participants gave written informed consent before taking part in the study.

Study Design and Measurements

Study participants were asked to continue on their usual diet for a run-in period of 4 weeks. Thereafter, participants were given written and verbal advice by specialist nurses on how to reduce salt, with a view to achieving an intake of ∼5 g daily. After an additional 2-week run-in period on reduced salt, individuals were then entered into a randomized, double-blind crossover study of slow sodium versus placebo tablets. They took 12 slow sodium tablets (10 mmol sodium per tablet) daily or 12 matched placebo tablets for 4 weeks each.

BP and other measurements were made at the end of each run-in period and at the end of each 4-week period on slow sodium or placebo. BP was measured by trained specialist nurses using an appropriate cuff size, with the arm at heart level, in the semisupine position, using a semiautomated device (OMRON HEM-705CP). The mean of the last 3 readings was recorded for analysis. Twenty-four–hour ambulatory BP (ABP) monitoring was performed using SpaceLab 90207 devices. They were fitted in the mornings, and ABP recordings were taken at half-hourly intervals during the day (from 9 AM to 10 PM) and at hourly intervals overnight (from 10 PM to 9 AM). Twenty-four–hour recordings were analyzed with the ABP report manager system (version 1.03.11) software package.

Laboratory Procedures and Statistical Methods

All blood samples were either analyzed immediately for routine assays or were spun and the plasma frozen and stored at −20°C until the time of assay. Plasma renin activity (PRA), aldosterone, and atrial natriuretic peptide (ANP) were measured by radioimmunoassay.28–30 Urine samples were also stored at −20°C until the time of assay. Total urinary protein was measured using a dye binding method as described previously.31

Group data for normally distributed variables are expressed as mean±SD, and we used the paired Student t test to compare differences between the slow sodium and placebo phases. Where variables were not normally distributed (eg, PRA, aldosterone, and ANP), the results are shown as the median and interquartile range, and the Wilcoxon sign ranks test was used. Correlation analysis was used for studying linear relationships between changes in variables with salt reduction. A (2-tailed) P value of <0.05 was regarded as statistically significant. All statistical tests were performed using SPSS 10.0 for Windows software.

Results

Baseline Characteristics

A total of 47 black hypertensives agreed to take part in the study. One withdrew during the run-in phase, and 6 dropped out after randomization, leaving a total of 40 black hypertensives (17 males and 23 females) who completed the study. Slow sodium and placebo were well tolerated, and no participants withdrew because of serious adverse reactions or events. The demographic characteristics of the 40 participants and their baseline BP and biochemical parameters, after the initial run-in period on the usual diet, are summarized in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50 (10)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79 (13)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28 (4)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>156 (12)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>100 (7)</td>
</tr>
<tr>
<td>Serum biochemistry</td>
<td></td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140 (2)</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.1 (0.3)</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>88 (18)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.0 (0.7)</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>43 (3)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.1 (0.8)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.0 (0.7)</td>
</tr>
<tr>
<td>PRA, ng/ml per hour*</td>
<td>0.10 (0.1–0.3)</td>
</tr>
<tr>
<td>Aldosterone, pmol/L*</td>
<td>287 (183–401)</td>
</tr>
<tr>
<td>ANP, pg/ml*</td>
<td>9.2 (6.1–13.7)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; GFR, glomerular filtration rate, calculated using the Cockroft–Gault formula. All values are expressed as the mean (SD) unless marked with an asterisk, in which values are median (interquartile range).

Effects of Salt Reduction on BP

The effects of slow sodium and placebo on urinary sodium excretion and BP are summarized in Table 2. The urinary sodium excretion on sodium tablets was 167±73 mmol per 24 hours, which is equivalent to a dietary salt intake of ∼10 g salt per day. The urinary sodium excretion on placebo tablets fell to 89±52 mmol per 24 hours, ∼5 g salt per day. Therefore, the mean fall in urinary sodium excretion was 78±62 mmol per 24 hours, equivalent to ∼5 g salt per day (P<0.001; Figure).

With this reduction in salt intake, BP fell from 159/101±13/8 to 151/98±13/8 mm Hg (ie, a fall in systolic pressure of 8±13 mm Hg [P<0.001] and diastolic pressure of 3±7 mm Hg [P<0.009]; Figure). In addition, there were significant falls in mean daytime and nighttime ABPs, with the reduction in salt intake (mean 24-hour reduction of 7±3 mm Hg).

Effects of Salt on Urine Protein Excretion

Urine protein excretion fell from 93±48 mg per 24 hours on slow sodium to 75±30 mg per 24 hours on placebo. Thus, the mean fall in urine protein excretion was 18±39 mg per 24 hours (P=0.008) with salt reduction (Figure). In addition, the mean urine protein to creatinine ratio fell significantly, from 6.6±3.2 to 5.7±2.2 mg per mmol (P=0.03).
Relationships Between Urine Protein Excretion, BP, and Urine Sodium Excretion

There was no significant relationship between the change in urine protein excretion and the change in systolic BP ($r=0.07$; $P=0.70$) or change in diastolic BP ($r=0.19$; $P=0.26$) with salt reduction. However, there was a highly significant correlation between the change in urinary protein excretion and the change in urine sodium excretion ($r=0.53$; $P=0.001$). This remained significant even when corrected for the fall in systolic and diastolic BP ($r=0.50$; $P=0.002$) and when corrected for BP as well as urinary potassium, urea, and creatine ($r=0.42$; $P=0.016$).

Effects of Salt on the Renin-Angiotensin System

There was a small but statistically significant increase in PRA, from 0.1 (0.1 to 0.3) ng/mL to 0.2 (0.1–0.4) ng/mL ($P=0.013$) with salt reduction. There was also a small, nonsignificant elevation in plasma aldosterone concentration.

Discussion

This is the first randomized, double-blind, placebo-controlled trial of salt reduction in black hypertensives. The results clearly demonstrate significant and important falls in BP (ie, an 8 mm Hg fall in systolic BP and 3 mm Hg fall in diastolic BP), with modest salt reduction from 10 to 5 g per day, this fall in BP was sustained over a 24-hour period, with significant falls in ABP measured in the day and at night. The achieved reduction in salt intake is from one that is similar to the current salt intake in most Western countries (10 to 12 g per day) to the WHO-recommended intake of ≤5 g per day.$^{32,27}$ With this reduction in salt intake, there was also a large and significant reduction in urine protein excretion of 19.4%.

Most previous studies of salt reduction in black individuals have been acute studies (ie, for ≤1 week) with large reductions in salt intake.$^{25,33,34}$ They have suggested that black hypertensives respond slightly better to salt reduction than white hypertensives as a result of their suppressed renin-angiotensin system.$^{25}$ The only other controlled but not double-blind trial of modest, longer-term reduction in salt intake is the DASH-sodium study.$^{24}$ It showed significant and dose-related falls in BP when salt intake was reduced from 8 to 6 and 4 g per day over a period of 1 month each. The fall in BP seen in the black group was slightly greater than in similar nonblack groups.$^{26}$ However, in the DASH-sodium study, all participants were given all food and drink, and how well individuals could stick to this diet on their own is not clear. The fall in BP that we have seen in the current double-blind study is equivalent to the fall seen with single drug therapy and also to that seen in previous double-blind studies in which we have shown that salt restriction is markedly additive to drugs that block the renin-angiotensin system.$^{35–37}$

There are no previous studies of the effect of salt reduction on urine protein excretion. Therefore, our findings are of...
considerable interest. Black hypertensives are more likely to develop hypertensive renal failure as well as being at greater risk from the direct cardiovascular effects of BP (ie, stroke, left ventricular hypertrophy, and cardiac failure).1–5 Proteinuria is known to be a major risk factor for the development and progression of renal disease as well as cardiovascular disease.8–11 This risk increases throughout the range of urine protein or albumin excretion and also applies to values within the normal range.36,39 The finding that salt reduction reduces urine protein excretion suggests that this will carry additional benefits on renal and cardiovascular risk in addition to that which would be obtained by BP reduction alone.

The reduction in urine protein excretion was related significantly to the fall in urine sodium excretion but not to the fall in BP. Observational studies, including the African American Study of Kidney Disease and Hypertension (AASK), showed a positive and significant correlation between 24-hour urinary sodium excretion and urine protein excretion in those who were screened for entry to the trial.40 Recent studies in white hypertensives have also demonstrated positive correlations between 24-hour urinary sodium excretion and target organ damage including microalbuminuria.19 These observational studies support the view that salt intake is a major risk factor for increased urine protein excretion, whereas our study shows that this risk can be reduced by a modest reduction in salt intake. However, not all BP-lowering therapies consistently reduce urine protein or albumin excretion. In the AASK study, treatment with amlodipine was associated with a significant increase in urine protein excretion from baseline, despite effective BP control, whereas ramipril and metoprolol reduced urine protein excretion.17

Some studies have suggested that there might be preferential effects of using drugs that block the renin-angiotensin system to lower proteinuria.15,16 It is of interest that in this study of salt restriction, the reduction in urine protein excretion occurred in the presence of a small but significant increase in the activity of the renin-angiotensin system. A previous short-term study showed that the antiproteinuric effects of an angiotensin-converting enzyme inhibitor could be abolished by increasing salt intake.41 It is likely then that there would be additive or even synergistic effects on urine protein excretion when the renin-angiotensin system is blocked at the same time as reducing salt intake.

Conclusion
A modest reduction in salt intake from 10 to 5 g per day reduced BP and urine protein excretion in nondiabetic black hypertensives.

Perspectives
Salt intake is a major cause of raised BP and risk factor for renal damage. WHO recommends that salt intake does not exceed 5 g per day.31 In this study, we demonstrated that a reduction in salt intake to this level is associated with a significant reduction in BP and urine protein excretion. In view of the continuous relationship between salt intake, BP, level of urine protein excretion, and renal and cardiovascular risk, our results demonstrate the potential long-term benefits of salt reduction on the progression of renal and cardiovascular disease in black individuals. We would speculate that these beneficial effects would also be seen in nonblack individuals. In addition, it is likely that the effects of salt reduction will be additive to the effects of inhibitors of the renin-angiotensin system on BP and urine protein excretion.

Our results illustrate the importance of giving simple clear advice to all black hypertensives on how to cut their salt intake from the current 10 to 12 g per day to <5 g/d.42

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References


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