Modest Salt Reduction Lowers Blood Pressure and Albumin Excretion in Impaired Glucose Tolerance and Type 2 Diabetes Mellitus
A Randomized Double-Blind Trial

Rebecca J. Suckling, Feng J. He, Nirmala D. Markandu, Graham A. MacGregor

Abstract—The role of salt restriction in patients with impaired glucose tolerance and diabetes mellitus is controversial, with a lack of well controlled, longer term, modest salt reduction trials in this group of patients, in spite of the marked increase in cardiovascular risk. We carried out a 12-week randomized double-blind, crossover trial of salt restriction with salt or placebo tablets, each for 6 weeks, in 46 individuals with diet-controlled type 2 diabetes mellitus or impaired glucose tolerance and untreated normal or high normal blood pressure (BP). From salt to placebo, 24-hour urinary sodium was reduced by 49±9 mmol (2.9 g salt). This reduction in salt intake led to fall in clinic BP from 136/81±2/1 mm Hg to 131/80±2/1 mm Hg, (systolic BP; P<0.01). Mean ambulatory 24-hour BP was reduced by 3±1/1 mm Hg (systolic BP, P<0.01 and diastolic BP, P<0.05), and albumin/creatinine ratio was reduced from 0.73 mg/mmol (0.5–1.5) to 0.64 mg/mmol (0.3–1.1; P<0.05). There was no significant change in fasting glucose, hemoglobin A1c, or insulin sensitivity. These results demonstrate that a modest reduction in salt intake, to approximately the amount recommended in public health guidelines, leads to significant and clinically relevant falls in BP in individuals who are early on in the progression of diabetes mellitus with normal or mildly raised BP. The reduction in urinary albumin excretion may carry additional benefits in reducing cardiovascular disease above the effects on BP. (Hypertension. 2016;67:1189-1195. DOI: 10.1161/HYPERTENSIONAHA.115.06637.)

Key Words: blood pressure ■ diet ■ hypertension ■ insulin ■ type 2 diabetes mellitus

Patients with diabetes mellitus die prematurely of cardiovascular disease. Macrovascular disease is often present at diagnosis of type 2 diabetes mellitus and a reduction in blood pressure (BP) lowers cardiovascular risk and increases patient survival.1 Evidence from genetic, epidemiological, migrational, intervention, treatment, and animal studies demonstrates that salt intake is important in regulating BP.2 Randomized trials have shown that a modest salt reduction lowers BP.3 However, participants in most previous studies did not have diabetes mellitus, and we found a limited number of trials with a modest reduction in salt intake, with the majority of trials involving short term, large changes in salt intake.4 Given the high cardiovascular risk in diabetes mellitus, the lack of well-controlled prospective studies of the effects of modest salt reduction in this group is surprising.

Increased evidence suggests that salt reduction may have additional beneficial effects on markers of cardiovascular disease. A reduction in salt intake lowers urinary albumin excretion, reduces left ventricular mass, and improves large artery compliance.5 Evidence from experimental studies suggests there may be a role for salt in the regulation of endothelial function.6 However, when translated to clinical studies, the effect of salt reduction on endothelial function has been inconsistent.7-10

We carried out a randomized controlled trial of modest salt reduction in individuals with diabetes mellitus or impaired glucose tolerance with normal or high normal BP. We aimed to determine the effects of a modest reduction in salt intake on BP, urinary albumin excretion, arterial stiffness, and markers of endothelial function.

Method

Participants
Individuals, between 30 and 80 years old, with diet-controlled type 2 diabetes mellitus or impaired glucose tolerance were recruited from the Blood Pressure Unit at St. George’s Hospital, London and from General Practice Surgeries in South London. Individuals were included with untreated sitting systolic BP between 120 and 170 mm Hg or diastolic BP between 70 and 100 mm Hg. Exclusion criteria were any secondary causes of hypertension, impaired renal function (plasma creatinine >150 μmol), uncontrolled heart failure, ischemic heart disease, previous stroke, active malignancy or liver disease, pregnancy, breast feeding, or taking the oral contraceptive...
pill. Those taking lipid-lowering therapy were included if prescribed for >3 months, and the dose remained unchanged during the study period. The study protocol was approved by Wandsworth Local Research Ethics Committee (LREC Approval Number: 06/Q0803/45) and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

**Study Design**

After 4 weeks of participant acclimatization, participants entered into a randomized double-blind crossover study (Figure 1). Baseline measurements were taken while on participants’ usual diet. Subsequently, participants were given detailed dietary advice by trained nurses to reduce salt intake to ≤5 g/d (90 mmol/d). Participants were advised not to add salt at the table or during cooking. Nurses identified food with high-salt content and advised them on low-salt alternatives. Where appropriate, the individual who prepared the food in the household was also seen. Salt-free bread was provided when required. Advice was reinforced at each visit for the duration of the study. After 2 weeks on the reduced salt diet, participants entered the randomized, double-blind crossover trial of salt versus placebo and remained on the reduced salt diet throughout the whole study. Randomization, using computer-generated random number sequences, was provided by an independent company, Healthspan Group Ltd who provided salt tablets and matching placebo tablets and had no other role in the running of the study. Participants received either 9 tablets of salt, each tablet containing 10 mmol, daily for 6 weeks or 9 matched placebo tablets, crossing over at the end of the 6-week period to take the opposite tablet for a further 6 weeks (Figure 1). All participants and research staff were blinded to treatment allocation.

**Measurements**

Measurements were performed at baseline and at the end of each 6-week study period. BP was measured by trained research nurses using a validated oscillometric technique (Omron HEM-705CP) in the sitting position after 5 to 10 minutes rest and using the same arm throughout the study. Three readings were taken at 1- to 2-minute intervals, and the mean of the last 2 readings were used for analysis. Twenty-four hour ambulatory blood pressure monitoring was performed using a SpaceLabs 90207 device (SpaceLabs, Inc, Washington, DC), fitted by an experienced research nurse. Monitoring was set to take measurements at half hourly intervals during the day and hourly intervals over night. Recordings were analyzed with the ambulatory blood pressure monitoring report manager system software package.

Two consecutive 24-hour urines were collected for the measurement of urinary sodium, potassium, calcium, creatinine, and albumin. The mean of the 2 urine measurements was used in the analysis.

Urinary albumin was measured by laser immunonephelometry using a Behring BN Prospec analyzer (Dade Behring) with within-assay imprecision of 1.4% to 3.5% and between-assay imprecision of 1.3% to 1.7%. Urine samples with measured concentration of <2.1 mg/L were reanalyzed using a high-sensitivity ELISA, with within-assay imprecision of 3.7% to 5.4% and between-assay imprecision of 4.1% to 6.3%. Blood samples were taken after an overnight fast (8–14 hours) for measurement of routine biochemistry, plasma renin activity, aldosterone, and insulin. Insulin sensitivity was assessed using the homeostatic model assessment, calculated as fasting plasma glucose (mmol/L) fasting serum insulin (μU/mL)/22.5.11

All vascular measurements were performed by a single trained operator after an overnight fast in a quiet temperature controlled room. Carotid-femoral pulse wave velocity was measured noninvasively using an automatic device (Compilor) as previously described and validated.12 Endothelial function was assessed by digital volume pulse analysis using a high-fidelity photo-plethysmography (PulseTrace1000, MicroMedical Ltd, Rochester, Kent, United Kingdom) to measure changes in the reflection index (RI) after salbutamol administration as a test of endothelial vasodulatory function and after glycerol trinitrate (GTN) as a test of endothelial-independent vasodilation.13 Baseline measurements were taken in triplicate at 5-minute intervals after subjects rested for 20 minutes. Sublingual GTN 500 mcg (Alpharma, Barnstable, Devon, United Kingdom) was administered for 3 minutes and recordings were made at 3, 5, 10, 15, and 20 minutes. After a rest of 10 minutes, albuterol 400 mcg (salbutamol, Baker Norton, London, United Kingdom) was administered via a spacer device, and recordings were repeated at 5, 10, and 15 minutes.14 This technique is validated for measuring endothelial function with a reproducibility for change in reflection index after albuterol (ΔRIAlb) of ~1.9±4.9% and after GTN (ΔRIGTN) of ~2.2±5.4%.15

**Statistical Analysis**

We calculated that 50 participants (allowing a 12% drop-out rate) were required to detect a difference in systolic BP of 5 mmHg between slow sodium and placebo, with a power of 90% and α=0.05, given a SD of 10. We used paired Student t test to compare the difference between salt and placebo for normally distributed variables and Wilcoxon signed-rank test for variables that were not normally distributed (ie, plasma renin activity, 24-hour urinary albumin, and albumin/creatinine ratio [ACR]). A 2-tail probability value of <0.05 was considered as statistically significant. All statistics were performed using Statistical Package for Social Science (SPSS).

Fifty-one individuals were recruited to the study of whom 46 completed the study. Two withdrew before randomization and 3 during the trial period with mean age of 48±5 years and mean baseline BP of 130/82±4/3 mmHg. There was no significant difference in baseline age and BP between participants who withdrew and those who...
completed the study. The results presented are based on analysis of data from the 46 individuals who completed the study.

**Results**

Of the 46 participants, 26 had type 2 diabetes mellitus and 20 had impaired glucose tolerance. Median duration from diagnosis of type 2 diabetes mellitus to study entry was 8 months (interquartile range, 3–12). Eight patients were taking lipido-lowering therapy and remained on the same dose throughout the study. At baseline (ie, on participants’ usual diet) the mean 24-hour urinary sodium was 138±7 mmol/24 hours, equivalent to 8 g/d salt. The average BP was 134±2/82±1 mm Hg. Other baseline characteristics, ambulatory blood pressure monitoring, and biochemistry data are summarized in Table 1.

During the randomized crossover phase, the mean 24-hour urinary sodium was 165.1±9.0 mmol/24 hours (9.7 g salt) on salt and 116.6±9.5 mmol/24 hours (6.8 g salt) on placebo. The reduction in salt intake was, therefore, 48.6±9.3 mmol (2.9 g salt) from salt to placebo. With this reduction in salt intake, BP fell from 135.5±2.0/81.3±1.1 mm Hg with salt to 131.2±1.9/79.7±1.2 mm Hg with placebo, that is, a fall of 4.2 mm Hg in systolic BP (P<0.01) and a fall in diastolic BP of 1.7 mm Hg (P=0.055), Figure 2. Results for ambulatory BP monitoring were available in 40 participants. These show similar results with significant falls in mean daytime, night time, and 24-hour BPs (Table 2; Figure 3).

Median ACR was 0.64 mg/mmol (interquartile range, 0.44–1.00) at baseline. ACR fell from 0.73 (interquartile range, 0.5–1.5) mg/24 hours on salt to 0.64 (interquartile range, 0.3–1.1) mg/24 hours on placebo (P=0.05), a reduction of 12%.

With salt reduction, measurements of insulin sensitivity were not altered, and there was no significant change in fasting glucose, hemoglobin A1c, insulin concentration, and homeostatic model assessment index. Salt intake did not alter total cholesterol (Table 2), LDL cholesterol (salt 3.43±0.2 mmol/L and placebo 3.48±0.2 mmol/L; P=0.416), HDL cholesterol (salt 1.30±0.06 mmol/L and placebo 1.29±0.05 mmol/L; P=0.644), or triglyceride levels (salt 1.56±0.12 mmol/L and placebo 1.65±0.13 mmol/L; P=0.316). There was a small increase in plasma renin activity and a small but significant increase in plasma creatinine (Table 2).

Pulse wave velocity and endothelial function were measured in 36 participants. Baseline pulse wave velocity was 12.7±0.4 m/s. There was no significant change in pulse wave velocity (12.8±0.4 m/s with salt and 12.6±0.4 m/s with placebo; P=0.57). Endothelial-dependent function, as measured by ∆RI_{LAG} was greater after placebo compared with salt, but this difference failed to reach significance (P=0.055; Table 3). Endothelial-independent function, as measured by ∆RI_{GTN} was greater than with salt although this difference was not significant. When placebo and salt periods were combined, change in reflection index after albuterol significantly correlated with 24-hour urinary sodium (r=0.235, P=0.036), indicating that when salt intake is lower, endothelial-dependent function is more responsive than when salt intake is higher.

**Discussion**

This study showed a modest reduction in salt intake, to the current level recommended by public health agencies, led to significant and clinically important reductions in BP.
function and although the improvement in endothelial function just failed to reach significance, those on the lowest salt intake had better endothelial function.

Type 2 diabetes mellitus and glucose intolerance are rapidly increasing throughout the world. With well-established relationships between elevated BP and increased cardiovascular risk, there has been a lack of well-controlled studies of the effects of a modest reduction in salt intake where the focus is on patients with type 2 diabetes mellitus and impaired glucose tolerance early on in their disease. Our study clearly shows that a reduction in salt intake, as currently recommended, has a significant effect on BP in individuals with type 2 diabetes mellitus and impaired glucose tolerance.

Table 2. Changes in Variables From Slow Sodium to Placebo in All Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Salt</th>
<th>Placebo</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic BP and Pulse (46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>135.5 (2.0)</td>
<td>131.2 (1.9)</td>
<td>−4.3±1.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>81.3 (1.1)</td>
<td>79.7 (1.2)</td>
<td>−1.6±0.9</td>
<td>0.055</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>54.2 (1.8)</td>
<td>51.6 (1.5)</td>
<td>−2.6±1.3</td>
<td>0.063</td>
</tr>
<tr>
<td>Sitting pulse (bpm)</td>
<td>68.9 (1.6)</td>
<td>69.3 (1.6)</td>
<td>0.4±1.2</td>
<td>0.726</td>
</tr>
<tr>
<td>Ambulatory BP, mmHg (40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h SBP</td>
<td>134.6 (2.0)</td>
<td>131.4 (1.8)</td>
<td>−3.3±0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>79.9 (1.4)</td>
<td>78.1 (1.3)</td>
<td>−1.8±0.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Day SBP</td>
<td>139.7 (2.2)</td>
<td>137.0 (1.9)</td>
<td>−2.7±0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Day DBP</td>
<td>84.2 (1.6)</td>
<td>82.7 (1.6)</td>
<td>−1.5±0.8</td>
<td>0.089</td>
</tr>
<tr>
<td>Night SBP</td>
<td>128.7 (1.9)</td>
<td>124.3 (1.7)</td>
<td>−4.4±1.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Night DBP</td>
<td>74.7 (1.3)</td>
<td>72.4 (1.2)</td>
<td>−2.3±0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urinary measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume, mL/24 h</td>
<td>1869 (119)</td>
<td>1811 (120)</td>
<td>57.6±95.4</td>
<td>0.549</td>
</tr>
<tr>
<td>Sodium, mmol/24 h</td>
<td>165.1 (9.0)</td>
<td>116.6 (9.5)</td>
<td>48.6±9.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Potassium, mmol/24 h</td>
<td>74.2 (4.3)</td>
<td>73.1 (4.8)</td>
<td>1.1±3.2</td>
<td>0.730</td>
</tr>
<tr>
<td>Creatinine, mmol/24 h</td>
<td>12.0 (0.59)</td>
<td>12.6 (0.7)</td>
<td>0.59±0.4</td>
<td>0.163</td>
</tr>
<tr>
<td>ACR, mg/mmol*</td>
<td>0.73 (0.5–1.5)</td>
<td>0.64 (0.3–1.1)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>95 (3)</td>
<td>94 (3)</td>
<td>0.3±0.3</td>
<td>0.218</td>
</tr>
<tr>
<td>Pulse wave velocity, m/s</td>
<td>12.6±0.4</td>
<td>12.8±0.4</td>
<td>0.17±0.29</td>
<td>0.57</td>
</tr>
</tbody>
</table>

(Continued)
Albuminuria predicts renal and cardiovascular complications in diabetes mellitus and short-term treatment induced reductions in albuminuria are associated with long-term renal and cardiovascular protection in diabetes mellitus. Increased cardiovascular risk continues throughout the range of albumin, with no threshold, independent of diabetic status and BP. Epidemiological studies have found a direct association between salt intake and urinary albumin. Modest salt restriction lowers urinary albumin excretion even when the levels are normal. A randomized controlled trial in 169 mild hypertensive individuals demonstrated that a reduction in salt intake by 3 g/d, lowered 24-hour urinary albumin by 11%. In black hypertensives, reducing salt intake by 5 g lowered 24-hour urinary protein by 19%. Findings from our study along with others suggest that salt reduction lowers urinary albumin excretion.

Although there is a general agreement that salt reduction is appropriate in hypertensive populations, hesitation in applying this recommendation in diabetic populations have been based on concerns of metabolic disturbance, including a meta-analysis claiming activation of the renin–angiotensin system and a rise in lipid levels. Evidence of metabolic disturbance is limited to studies with large changes in salt restriction, such as changing salt intake from 20 to 0.5 g/d. More modest reduction in salt intake lead to small, physiological increases in plasma renin activity and aldosterone and do not effect lipid levels. We have demonstrated in this study that a modest reduction in salt intake shows small increases in renin with no significant change in aldosterone, cholesterol, or measurements of insulin resistance.

Pulse wave velocity did not improve in this study. In 169 individuals with mild hypertension, a reduction in salt intake of 3 g/d lowered pulse wave velocity principally in black hypertensives, despite larger changes in dietary salt in whites and Asians. Modest salt reduction in 29 obese normotensive individuals did not improve arterial stiffness, despite changes
in endothelial function, and authors suggested the duration of study was an important factor. The duration of salt restriction, body weight, predominantly white group and low baseline BP may account for the lack of improvement in pulse wave velocity with modest salt reduction seen in this study.

While randomized controlled trials have varied in quality, duration, and intervention, they have reported a relatively consistent dose-dependent decrease in BP with reduction in salt intake. Previous studies in nondiabetic populations have demonstrated a reduction in cardiovascular events when salt intake was reduced. A recent observational study in patients with type 2 diabetes mellitus found that lower salt intake was paradoxically associated with an increase in cardiovascular mortality. Methodological limitations, particularly with 24-hour urine collection, and the characteristics of the study population limit the applicability of these findings.

The positive association between 24-hour urinary sodium and endothelial-dependent function assessed with albuterol suggests that in conditions of high-salt intake endothelial function is less responsive. In experimental studies, low-salt intake improves endothelial function through increases in nitric oxide production. Using cultured bovine aortic endothelial cells, Oberleithner et al showed that an increase in sodium concentration in the culture medium, within the physiological range, increased endothelial cell stiffness and reduced activity of endothelial nitric oxide synthase. Findings in clinical studies have been less consistent. With a modest salt reduction of 5 g/d >2 weeks, endothelial-dependent vasodilatation improved by 45% in a small study of normotensive obese subjects. Others have not demonstrated salt-dependent changes in endothelial function, although large changes in salt intake may have stimulated compensatory mechanisms affecting the endothelial response.

This study has several limitations. The study size was small and was not designed to describe differences between degree of insulin resistance, ethnicities, or sex. Analysis of 34 trials, including 3230 participants, showed significant reduction in BP in both men and women and in both black and white patients. Although the study was performed in a specialist BP unit, with research nurses experienced in providing advice to reduce salt intake, the reduction of salt intake from baseline was small and the difference in salt intake between the salt and placebo was only 3 g. This is due to the high prevalence of salt in food, particularly in baked and processed food, which makes it a challenge to achieve a reduction in salt intake, even in highly motivated patients taking part in a clinical trial.

### Perspectives

Worldwide, it is predicted that there will be a global rise in the number of people with diabetes mellitus from 171 million people in 2010 to 366 million by 2030. Macrovascular disease is often present at diagnosis of type 2 diabetes mellitus. The focus should be on studying strategies to prevent these cardiovascular complications earlier in the course of the disease. Our study demonstrates that a modest, achievable reduction in salt intake leads to clinically and statistically significant falls in BP. Additional benefits of salt reduction were found with a fall in ACR. These results suggest that reducing salt intake to the recommended levels of 5 to 6 g/d would lower BP and reduce the risk of cardiovascular disease irrespective of the BP level.

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