ORIGINAL ARTICLE

Salt restriction among hypertensive patients: Modest blood pressure effect and no adverse effects

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Abstract

Objective. Previous studies, mainly evaluating short-term very low salt diets, suggest that salt restriction may influence glucose and insulin metabolism, catecholamines, renin, aldosterone, and lipid levels adversely. The authors wanted to explore whether sodium restriction for eight weeks influenced insulin secretion unfavourably, and evaluate the efficacy and safety of such treatment also in terms of other parameters important in the management of hypertensive patients. **Design.** A double-blind randomized controlled parallel group designed trial. All participants received dietary advice aimed at a moderate salt-restricted diet. Half of the participants received salt capsules, the others received identical placebo capsules. **Setting.** General practice. **Subjects.** Forty-six hypertensive patients inadequately controlled by drug treatment. **Main outcome measures.** Fasting serum insulin C-peptide and glucose and levels of these measures after oral glucose, blood pressure, serum aldosterone and lipids, peripheral resistance, and skin conductance. **Results.** Salt restriction did not influence glucose and insulin metabolism, aldosterone, or lipid levels adversely. We observed better blood pressure regulation in the low salt group than in the high salt group, with a systolic and diastolic blood pressure difference of 5/5 mmHg after eight weeks. The difference was only statistically significant for diastolic blood pressure, p 0.02. **Conclusion.** This study revealed a modest diastolic blood pressure reducing effect of moderate sodium restriction. This reduction was obtained without any apparent unfavourable side effects such as increased insulin secretion, impaired glucose tolerance or dyslipidaemia.

Key Words: *Diet, family practice, hypertension, insulin resistance, lipids, sodium-restricted*

Hypertension is associated with disturbances of lipid and glucose metabolism [1]. Insulin resistance seems to play a key role in the metabolic aberrations related to the hypertensive state [2]. Although salt restriction is still considered controversial as a measure for prevention of hypertension [3], greater agreement exists concerning salt-reduced diets as a treatment option for patients with established hypertension [4]. However, it remains unclear whether such treatment will benefit patients regarding significant outcomes. Although a few reports show effects on hard endpoints from sodium restriction [5] or replacement [6], the effect and safety of such treatment must still rely on surrogate endpoints.

Reports, mainly evaluating short-term very low salt diets, suggest that salt restriction may influence glucose and insulin metabolism, catecholamines, renin, aldosterone and lipid levels adversely [4,7–9].

Earlier research suggests that salt restriction may influence glucose and insulin metabolism, aldosterone, and lipid levels adversely.

- This paper demonstrates that a modest blood pressure reduction is achieved by an eight-week moderate salt-reduced diet without such unwanted side effects.

Adverse effects are also reported from long-term trials [10–12], but such effects are insignificant or absent in the majority of such trials [4,12–18].

According to Graudal [4], the question as to whether sodium restriction affects hormone and lipid profiles unfavourably remains inconclusive. He therefore calls for long-term trials of sodium

restriction as a prophylactic or treatment strategy. In a previous open pretest–posttest study among treated and untreated hypertensive patients, we observed a 40% increase of insulin C-peptide during 12 weeks of moderate salt restriction [19]. This observation was not replicated in a controlled clinical trial with crossover design [17]. In our first study we observed that patients on drug treatment responded more disadvantageously regarding insulin production than others. Our second study was performed on hypertensive patients without drug treatment, and the crossover design might also minimize the effects that we set out to explore [17].

Against this background, we wanted to explore whether sodium restriction for eight weeks influenced insulin secretion unfavourably, and evaluate the efficacy and safety of such treatment also in terms of other parameters important in the management of hypertensive patients inadequately controlled by drug treatment.

Material and methods

The study comprised patients on antihypertensive drug treatment aged 20–75 years with diastolic or systolic blood pressure readings in excess of 90 mmHg and/or 160 mmHg on two occasions during a run-in period of at least three weeks' duration. A total of 71 patients were evaluated during 1999–2002 as candidates for the study. Nineteen patients did not satisfy the blood pressure inclusion criteria on the first or the inclusion visit, and two persons withdrew during the run-in period for unknown reasons.

Exclusion criteria included possible drug-induced hypertension (e.g. NSAIDs and oestrogen), cardiovascular disease necessitating drugs with hypotensive effect, and blood pressure increase to a level of >115 mmHg diastolic or 210 mmHg systolic before or during the study. None was excluded, but four patients withdrew during the study for unknown reasons, and were replaced by others according to the same inclusion and randomization procedures.

Forty-six hypertensive patients (34 men and 12 women) with a mean age of 56 were included in the study. Their characteristics are summarized in Table I. After a run-in period of at least three weeks' duration, participants were randomly assigned to one of two groups. Both groups were provided dietary advice outlining a moderate salt-reduced diet [20]. Group A ($n=23$) received NaCl capsules (five capsules of 10 mmol sodium per day corresponding to the expected salt reduction from a moderate salt-restricted diet); group B ($n=23$) received identical placebo capsules (five capsules SiO_2 per day). The groups were examined over

eight weeks in a parallel group-designed trial after four weeks and at the termination of the study.

Measurements and procedure

A simple randomization procedure ensuring equal numbers in the two groups was performed. The randomization list was concealed and kept inaccessible to the investigators during the trial, and was disclosed after all the statistical analyses had been conducted. The capsules were kept in sealed envelopes with a patient number that was in accordance with the randomized sequence.

Blood pressure was measured with a mercury manometer on the right arm in a sitting position after a minimum of two minutes' rest. Three recordings were performed at two-minute intervals, with the mean of the last two readings used for analyses. Cuffs of adequate size for the circumference of the arm were provided, and the same cuff was used on each visit. Each patient's height and weight were measured at inclusion, and weight measurement was repeated at the termination of the study. Participants were discouraged from losing weight or changing exercise habits during the study.

Blood pressure readings were performed before run-in, at inclusion, and after four and eight weeks. Patients also met the study investigators for dietary advice, compliance assessment, and provision of salt/placebo capsules. At inclusion and the final visit, resting pulse per minute was assessed after six minutes' rest. Following the resting pulse assessment, skin conductance was measured on the palmar side of the third and fourth mid-phalanxes of the dominant hand. Skin conductance seems a valid measure of sympathetic stress [21]. A lower level of micro-siemens (μmho) indicates a greater sympathetic activity. Total peripheral resistance was estimated indirectly according to the formula:

$$\text{DiaBP} + (\text{SysBP} - \text{DiaBP}) / 3 / (\text{SysBP} - \text{DiaBP}) * 2 * \text{PULSE}.$$

After four weeks and at the final visit, returned capsules were counted for compliance assessment. At the final visit, participants were asked if they knew the content of the provided capsules. Three alternatives were noted: "salt capsules", "capsules without salt", and "do not know the content".

Participants attended each control at the same time after overnight fasting. At inclusion and the final visit, they brought with them a sample of 24 h urine for measurement of sodium, chloride, and potassium excretion. These measurements together with capsule counts were used as a control of dietary compliance. Fasting insulin C-peptide and glucose were measured and also assessed after 30 minutes

Table I. Characteristics at inclusion of 46 drug-treated hypertensive patients (23 in each study group) with inadequately controlled hypertension.

Variable	Salt-supplemented group Mean or proportion	Placebo group Mean or proportion	95% CI of mean or proportional difference
Age (yrs)	55	57	-1.8, 2.3
Body Mass Index	29	29	-2.2, 3.7
24 h urine sodium secretion (mmol)	98	93	-19, 29
Systolic blood pressure (mmHg)	155	157	-11, 6
Diastolic blood pressure (mmHg)	92	93	-5, 4
Fasting se-glucose (mmol/l)	5.5	6.6	-2.2, 0.1
Se glucose after oral glucose (mmol/l)	8.9	10.3	-3.0, 0.1
Fasting insulin-C-peptide (nmol/l)	1.2	0.9	-0.1, 0.5
Insulin-C-peptide after oral glucose (nmol/l)	2.0	1.8	-0.1, 0.5
Total se-cholesterol (mmol/l)	6.1	6.4	-0.9, 0.5
Se-HDL-cholesterol (mmol/l)	1.2	1.3	-0.3, 0.1
Se-triglyceride (mmol/l)	2.2	1.7	-0.2, 1.4
Skin conductance (μ mho)	1.2	1.2	-0.5, 0.3
Total peripheral resistance	266	262	-45, 53
Female gender	0.26	0.26	-0.25, 0.25
On thiazide diuretics	0.78	0.57	-0.05, 0.48
On beta-blockers	0.35	0.26	-0.18, 0.35
On ACE inhibitors	0.17	0.17	-0.22, 0.22

following a 75 g oral glucose load. Samples were drawn for the measurement of fasting lipids: total cholesterol, HDL cholesterol, and triglycerides. Samples for the assessment of urine electrolytes, insulin C-peptide, aldosterone, and serum lipids were kept frozen at -80°C , and were analysed in one run to reduce analytic variance and accidental insufficiencies.

Analysis of cholesterol, HDL cholesterol, triglyceride, and glucose in serum was performed on an automated commercial routine analyser, Modular from Roche Diagnostics GmbH, Germany, with analytical coefficients of variation (CV) of 2%, 3%, 2%, and 1.5% respectively. Potassium, sodium, and chloride in urine were analysed by ion-selective electrodes in the Modular from Roche Diagnostics GmbH, Germany, with analytical CV of 1–2%. Aldosterone was determined using the Coat-A-Count® Aldosterone radioimmunoassay from Diagnostic Products Corporation (Los Angeles, CA, USA) for quantitative measurement in unextracted serum, with an intra-assay CV of 2.9–5.4% for the concentration range 1600–180 pmol/l. Insulin C-peptide was measured using a luminescence enzyme immunoassay (LIA) method: IMMULITE 2000 C-Peptide from Diagnostic Products Corporation (DPC) with a within-run CV for 3.02 nmol/l of insulin C-peptide of 7.0% and 14.1% for 0.74 nmol/l of insulin C-peptide.

Statistics

Statistical tests were performed using SPSS/PC V 13.0. Descriptive analyses were used to compute

means and confidence intervals (CI). The differences from inclusion in the study to the mid- and final treatment period were computed for every participant, and comparisons between the two groups were evaluated using t-tests for independent samples. If the distributions of the measures were strongly skewed (skewness >1 or <-1), Mann-Whitney-U tests were performed. The study was designed with a power of 0.75 and significance level of 0.05 to detect a 30% difference in change of insulin C-peptide from 1.61 microg/l (SD 0.6 microg/l was assumed) following salt restriction. Results are presented with means and 95% CI. Two-tailed tests were used and significance was accepted at the 0.05 level. We calculated the mean between group differences that we could rule out based on the participants and observations from the present study, with power and significance levels of 80% and 5% respectively. A blood pressure difference of 12/6 mmHg, aldosterone difference greater than 300 pmol/l, fasting insulin C-peptide difference greater than 0.4 nmol/l, total and HDL cholesterol differences greater than 0.9 and 0.3 mmol/l respectively, and triglyceride and glucose differences greater than 1.1 and 1.7 mmol/l could be ruled out.

Ethics

All patients gave their informed consent, and the study was approved by the Regional Committee for Medical Research Ethics, Health Region III. Both investigators are independent of funders.

Results

As shown by Table I, the randomization was effective, although borderline significant differences were revealed concerning fasting serum glucose levels and following an oral glucose load. All other differences were statistically insignificant (p -values >0.1). Medications with suspected influence on glucose tolerance were similar in the two groups.

Controlling for blinding in the study, we revealed that participants often identified the content of the capsules ($p < 0.0005$). Insufficient blinding was often due to gastrointestinal complaints following salt intake. We counted the returned capsules and found that the daily intake averaged 4.1 capsules in both groups, corresponding to 41 mmol of sodium in the group provided with salt. The capsule intake compliance was therefore relatively good, as also confirmed by Table II demonstrating a 38 mmol difference in 24 h urine sodium excretion between the groups. Participants in both groups already recorded relatively low sodium excretion at inclusion, and the dietary advice contributed only slightly to a further decrease in the placebo group. Body weights were kept constant in both groups.

Table II shows that only diastolic blood pressure changed significantly after eight weeks. The significance of these differences must be interpreted with caution as the study was designed with insulin C-peptide as the primary outcome measure.

Table III shows between-group differences of changes regarding important measures of claimed unwanted side effects of salt restriction. We were unable to detect any statistically significant between-group differences concerning these measures.

Discussion

In this trial we observed more favourable blood pressure regulation in the low salt group compared with the high salt group. The difference was,

however, only statistically significant for diastolic blood pressure. The primary objective of this study was to examine whether sodium restriction impaired insulin C-peptide or glucose levels. We could not detect such an impairment following a salt-reduced diet over eight weeks. The sodium restriction that the present study imitated was modest, and we cannot rule out unfavourable changes from more substantial reductions of sodium intake.

The major weakness of the study was a somewhat inferior statistical power of 75%. Strengths of the study were its eight-week evaluation; a moderate difference in salt intake (≈ 40 mmol per day) attainable in an outpatient setting [20]; the parallel group design; the general practice setting; that we performed a control of blinding; and the comprehensive evaluation of several measures that are important in the management of hypertension.

The blood pressure effects are similar or slightly in excess of the results from similar studies among Caucasians with elevated blood pressure [4]. The salt-supplemented group, imitating a high normal sodium content in everyday diet, had the most unfavourable change of glucose levels. Although the difference was insignificant ($p = 0.12$), the change was in the opposite direction from what we might have expected on the basis of some former studies [9,19,22–24]. Only studies measuring acute effects after oral or intravenous ingestion of sodium, or salt restriction combined with cardio-protective diets, have demonstrated beneficial effects on insulin resistance [25–27].

Insulin C-peptide is an adequate measure of endogenous insulin production. Hyperinsulinaemia is linked with insulin resistance, and has been identified as an independent risk factor for cardiovascular disease [28] and non-insulin-dependent diabetes [29]. It is therefore important to clarify to what extent such diets may result in increased insulin production. The studies claiming adverse effects on glucose tolerance or insulin sensitivity

Table II. Urine electrolyte secretion, body weight, and blood pressure changes after four and eight weeks on a moderate salt-restricted diet with double blind provision of salt or placebo capsules in the two study groups (values at four and eight weeks are subtracted from inclusion values).

Variable	Salt-supplemented group, mean difference compared with inclusion	Placebo group, mean difference compared with inclusion	95% CI of mean difference (p -value ¹)
Na ⁺ excretion after 8 weeks (mmol)	–28	10	–84, 9 (0.11)
K ⁺ excretion after 8 weeks (mmol)	3	–9	–1, 26 (0.08)
Body weight (kg)	–1	0	–2, 0.5 (0.2)
Systolic blood pressure after 4 weeks (mmHg)	–1	2	–9, 3 (0.3)
Diastolic blood pressure after 4 weeks (mmHg)	0	2	–6, 1 (0.1)
Systolic blood pressure after 8 weeks (mmHg)	0	5	–11, 0 (0.07)
Diastolic blood pressure after 8 weeks (mmHg)	–2	3	–7, –1 (0.02)

¹t-test for independent samples.

Table III. Between-group differences of changes relating to important measures of claimed unwanted side effects of salt restriction after eight weeks on a moderate salt-restricted diet with double-blind provision of salt or placebo capsules (values at eight weeks are subtracted from inclusion values).

Variable	Salt-supplemented group, mean difference compared with inclusion	Placebo group, mean difference compared with inclusion	95% CI of mean difference (p-value)
Fasting se-glucose (mmol/l)	-0.2	-0.1	-0.5, 0.3 (0.5 ¹)
Se glucose after oral glucose (mmol/l)	-0.5	0.1	-1.4, 0.2 (0.12 ¹)
Fasting insulin-C-peptide (nmol/l)	0.03	0.04	-0.28, 0.26 (0.6 ²)
Insulin-C-peptide after oral glucose (nmol/l)	-0.05	-0.09	-0.15, 0.23 (0.7 ¹)
Total se-cholesterol (mmol/l)	0.0	0.2	-0.6, 0.3 (0.4 ²)
Se-HDL-cholesterol (mmol/l)	0.00	0.05	-0.25, 0.15 (0.9 ²)
Se-triglyceride (mmol/l)	-0.2	0.1	-0.6, 0.2 (0.3 ¹)
Se-aldosterone (pmol/l)	34	96	-236, 111 (0.4 ²)
Skin conductance (μmho)	0.24	0.01	-0.11, 0.56 (0.13 ²)
Total peripheral resistance	-23	3	-58, 6 (0.11 ¹)

¹t-test for independent samples; ²Mann-Whitney U-test.

following sodium restriction are without exception short-term trials with vast differences in sodium intake [8,9,22–24,30,31]. Some investigators maintain that a threefold reduction of sodium intake still impaired insulin sensitivity after one week [24], whereas Fliser and co-workers demonstrated that the hyperinsulinaemic response to severe salt depletion attenuated and disappeared over three to seven days [8]. Studies with longer-term moderate salt-reduced diets are in line with the present study [15,16], and also confirm the results of our former crossover trial [17]. Accordingly, the evidence unambiguously contradicts that longer-term moderate salt-reduced diets influence insulin sensitivity unfavourably.

Increase of peripheral resistance has been reported in a previous long-term trial [32]. In the present study we estimated vascular resistance indirectly, and could not find any between-group difference. Increased sympathetic activity, especially increase of noradrenaline excretion, has also been reported following short-term severe salt depletion [4,8,33]. On the other hand, in long-term studies, no significant changes or decreased levels of catecholamines have been detected [4,34,35]. In the present study, measuring sympathetic tonus by skin conductance, no statistically significant between-group difference was observed.

Similar patterns arise concerning aldosterone and renin secretion following salt-reduced diets: increased levels are detected following short-term severe depletion [4,33,36], while long-term moderation of salt intake only exceptionally leads to increased aldosterone–renin activity [4,11,34,37,38]. No significant between-group difference in serum aldosterone level was detected in the present trial.

Increased levels of total and LDL cholesterol are reported in the Cochrane review by Graudal and co-

workers [4], but in this case too studies evaluating long-term effects of salt moderation are unable to detect significant dyslipidaemic effects [4,12]. In line with this, we were unable to detect any unfavourable effects on serum lipids or atherogenic index in either the present or the previous crossover study we performed [17].

In conclusion, this study revealed a modest diastolic blood pressure reducing effect of moderate sodium restriction. This reduction was obtained without any apparent unfavourable side effects concerning insulin secretion, impaired glucose serum levels, or dyslipidaemia, but the power of the study was somewhat inadequate to draw firm conclusions. The present study is, however, in line with other longer-term trials with moderate salt restriction showing no adverse side effects.

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