A Low-Sodium Diet Potentiates the Effects of Losartan in Type 2 Diabetes

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OBJECTIVE — Diabetic subjects have a high prevalence of hypertension, increased total body exchangeable sodium levels, and an impaired ability to excrete a sodium load. This study assessed the effect of dietary sodium restriction on the efficacy of losartan in hypertensive subjects with type 2 diabetes and albumin excretion rates of 10–200 μg/min.

RESEARCH DESIGN AND METHODS — In this study, 20 subjects were randomized to losartan 50 mg/day ($n = 10$) or placebo ($n = 10$). Drug therapy was given in two 4-week phases separated by a washout period. In the last 2 weeks of each phase, patients were assigned to low- or regular-sodium diets, in random order. In each phase, 24-h ambulatory blood pressure, urinary albumin-to-creatinine ratio (ACR), and renal hemodynamics were measured.

RESULTS — Achieved urinary sodium on a low-sodium diet was 85 ± 14 and 80 ± 22 mmol/day in the losartan and placebo groups, respectively. In the losartan group, the additional blood pressure−lowering effects of a low-sodium diet compared with a regular-sodium diet for 24-h systolic, diastolic, and mean arterial blood pressures were 9.7 mmHg (95% confidence interval [CI], 2.2−17.2; $P = 0.002$), 5.5 mmHg (2.6−8.4; $P = 0.002$), and 7.3 mmHg (3.3−11.3; $P = 0.003$), respectively. In the losartan group, the ACR decreased significantly on a low-sodium diet versus on a regular-sodium diet (−29% [CI −50.0 to −8.5%] vs. +14% [−19.4 to 47.9%], respectively; $P = 0.02$). There was a strong correlation between fall in blood pressure and percent reduction in the ACR ($r = 0.7$, $P = 0.02$). In the placebo group, there were no significant changes in blood pressure or ACR between regular- and low-sodium diets. There were no significant changes in renal hemodynamics in either group.

CONCLUSIONS — These data demonstrated that a low-sodium diet potentiates the antihypertensive and antiproteinuric effects of losartan in type 2 diabetes. The blood pressure reduction resulting from the addition of a low-sodium diet to losartan was of similar magnitude to that predicted from the addition of a second antihypertensive agent.

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High blood pressure is an important modifiable risk factor in preventing diabetic micro- and macrovascular complications. Subjects with diabetes have a high prevalence of hypertension and often require multiple antihypertensive agents to achieve blood pressure targets (1).

The role of ACE inhibitors in the prevention and treatment of diabetic nephropathy is well established in patients with type 2 (2) and type 1 diabetes (3). More recently, blockade of the renin-angiotensin system (RAS) with angiotensin (ANG)-II receptor antagonists has been shown to attenuate the rate of progression of renal dysfunction in patients with type 2 diabetes (4,5).

In nondiabetic subjects with renal disease, the antiproteinuric effects of ACE inhibitors strongly depend on dietary sodium intake (6). Furthermore, the antihypertensive effects of ANG-II receptor antagonists have shown dependence on the baseline activation of the RAS in nondiabetic patients (7). In diabetic subjects studied over 12 months on their usual sodium diets, the level of dietary sodium was found to interfere with ACE inhibitors' ability to lower blood pressure (8). Studies in experimental diabetes indicate that sodium restriction has favorable effects on glomerular filtration rate (GFR), kidney weight, albuminuria, and blood pressure (9) and that high-sodium intake blocks the antiproteinuric effects of ACE inhibition (10).

Dietary sodium restriction, used alone or combined with other drug therapy, has been clearly demonstrated to play an important role in the management of hypertension in the nondiabetic population (11–13). Diabetic patients differ from the nondiabetic population by having an increase in total body sodium (14,15), an increase in renal tubular sodium reabsorption, and an impaired ability to excrete a sodium load (16). These factors suggest that dietary sodium intake may potentially play a greater role in the management of hypertension in the diabetic population. Inadequate suppression of the RAS has been put forward as a mechanism for the high prevalence of hypertension, salt sensitivity of blood

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Abbreviations: ABP, ambulatory blood pressure; ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; ANG, angiotensin; CI, confidence interval; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; PAH, para-aminohippurate; P_{GC}, glomerular capillary pressure; PRA, plasma renin activity; RAS, renin-angiotensin system.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

M.E.C. is on an advisory panel for Merck on diabetic nephropathy, he has received honoraria for speaking engagements for Merck, and his laboratory has received funding from Merck for studies on a new drug to treat retinopathy.

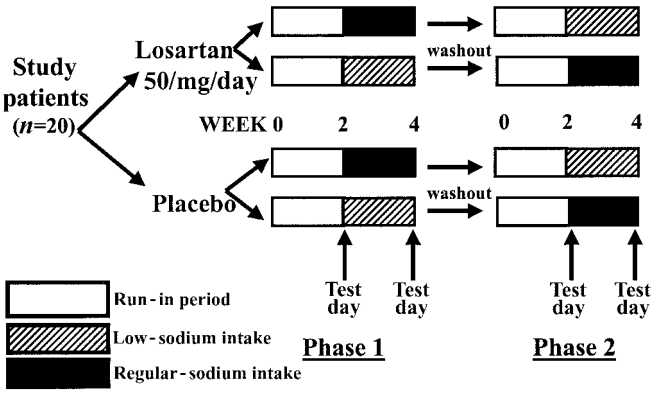

Figure 1—*Study protocol.*

pressure, blunted renal hemodynamic responses to varying sodium intakes (17), and renal damage in type 2 diabetic subjects (18).

This prospective, randomized, double-blind, dietary crossover study sought to evaluate the antihypertensive, antiproteinuric, and renal hemodynamic effects of combination therapy with a low-sodium diet and the ANG-II-receptor antagonist, losartan, in subjects with hypertension, elevated albumin excretion rate (AER), and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients

We studied 20 patients with type 2 diabetes, hypertension, and albuminuria of 10–200 μg/min on an ambulatory basis. Participants were recruited from the Austin and Repatriation Medical Center diabetes clinic as well as the surrounding district. Inclusion criteria included a diagnosis of type 2 diabetes, age 30–75 years, seated systolic blood pressure >130 mmHg and/or seated diastolic blood pressure >85 mmHg, AER 10–200 μg/min, HbA_{1c} <11.0% (normal 4.3–6.1%), an absence of serious systemic illness, an absence of history of substance abuse, and habitual 24-h urinary sodium excretion >100 mmol/24 h. Exclusion criteria included seated systolic blood pressure >165 mmHg or diastolic blood pressure >100 mmHg, serum potassium >5.5 mmol/l, plasma creatinine >200 μmol/l, long-term use of nonsteroidal anti-inflammatory drugs, a history of recurrent urinary tract infections (more than three per year), BMI >35 kg/m^2, cardiac failure, nitrate therapy, or intolerance of ACE inhibitors. Antihypertensive or diuretic therapy was stopped for at least 2 weeks before commencing the study. This allowed for a complete washout of prior antihypertensive agents.

The study was approved by the Human Research Ethics Committee at the Austin and Repatriation Medical Center, and all patients gave informed consent before commencement of the study.

Study protocol

The study protocol is outlined in Fig. 1. In this placebo-controlled dietary crossover study, patients were studied on regular- and low-sodium intakes, with each patient acting as his or her own control. The power of the study was based on the assumption that blood pressure would be estimated with a SD of 8 mmHg. To detect a difference between regular- and low-sodium diets of 1 SD, with a power of 80% and an α of 5%, paired data in 10 subjects were required (19). Patients were randomly assigned in a double-blind fashion to receive losartan 50 mg/day (n = 10) or a matching placebo (n = 10). This medication was taken daily for two 4-week phases with a 4-week washout period between phases. There was no crossover in medication assignment. Patients remained on their usual diets during a 2-week run-in period and were then assigned, in random order, to a 2-week dietary period of either restricted sodium intake (target 50–70 mmol/day) or continuation of regular sodium intake (>100 mmol/day). In the second phase, there was a crossover in dietary assignment. Low-sodium diets were conducted on an ambulatory outpatient basis. Patients received advice from a clinical nutritionist and subsequently brought and prepared their own food. They were provided with no-added-salt bread for the low-sodium period.

The terms $losartan_{RS}$ and $losartan_{LS}$ were used to refer to the 2-week period, from weeks 2 to 4, in which subjects in the losartan group were assigned to regular- and low-sodium diets, respectively. The terms $placebo_{RS}$ and $placebo_{LS}$ were used to refer to the 2-week period, from weeks 2 to 4, in which subjects in the placebo group were assigned to regular- and low-sodium diets, respectively. After the washout period, patients entered the study protocol if sitting systolic and/or diastolic blood pressures (mean of three readings) were >130 and/or >85 mmHg, respectively.

Parameters measured at weeks 2 (after medication run-in) and 4 (after the 2-week dietary period) included 24-h ambulatory blood pressure (ABP), GFR, and effective renal plasma flow (ERPF). Parameters measured at weeks 0, 2, and 4 included body weight, albumin-to-creatinine ratio (ACR) on 24-h urine collection, plasma glucose, electrolytes, plasma renin activity (PRA), ANG-II, and aldosterone. Urinary electrolytes, urea, and creatinine were determined at baseline and weekly during each phase. All biochemical analyses were performed in the morning after patients fasted overnight and before they took the study medication. Measurement of GFR and ERPF was begun 1 h after medication was administered. Measurement of 24-h ABP at week 0 was obtained in a subset of 12 patients.

The 24-h ABP was measured with a portable recording system (Spacelabs 90207; Spacelabs Medical Products, Deerfield, WI) based on an oscillometric method. The 24-h systolic, diastolic, and mean arterial pressures as well as wake and sleep values were recorded. Blood pressure was measured every 30 min from 7:00 A.M. to 11:00 P.M. and every hour from 11:00 P.M. to 7:00 A.M.

Laboratory methods

Radioimmunoassay for albumin was performed by a double-antibody method with intra- and interassay coefficients of variation of 1.8 and 4.8%, respectively, for a sample concentration of 27 mg/l. The determination of creatinine in plasma and urine was performed by the modified Jaffé method (kinetic colorimetric assay). Plasma creatinine and electrolytes were

measured on a Hitachi 747 Auto Analyzer (Roche Diagnostics, Mannheim, Germany), and urinary creatinine and electrolytes were measured on a Hitachi 911 automatic analyzer (Roche Diagnostics). HbA_{1c} was determined by boron affinity chromatography on a Primus CLC330 analyzer (Kansas City, MO).

Specimens for PRA and ANG-II were collected in EDTA tubes on ice, centrifuged within 1 h, and stored at –20°C for analysis at a later date. Plasma ANG-II was measured by direct radioimmunoassay. PRA was determined by measuring the rate of generation of ANG-I by radioimmunoassay after incubating plasma at 37° for 1 h. Plasma aldosterone was measured by direct radioimmunoassay (Coat-A Count Aldosterone; Diagnostic Products, Los Angeles, CA).

Renal hemodynamics

GFR was measured by the plasma clearance of nonradioactive iohexol after a single bolus intravenous injection. Plasma concentrations of iohexol were measured by capillary electrophoresis (20), and GFR calculations were performed using the Brochner-Mortensen corrected one-compartment model, as previously described (21).

ERPF was measured using ^{99m}Tc-MAG-3. A single dose of 10 MBq of ^{99m}Tc-MAG-3 was injected as an intravenous bolus, and 11 blood samples were taken over the ensuing 90 min (22). The plasma clearance was fitted to a bi-exponential model using an iterative non-linear regression curve-fitting program (Sigmaplot; Scientific Graphing Software, Jandel Scientific, CA). ERPF is reported as MAG-3 clearance values. All GFR and ERPF measurements were corrected for body surface area and are expressed as milliliters per minute per 1.73 meters squared.

The filtration fraction (FF)—the filtered proportion of the renal blood flow—was calculated by the equation FF = GFR × 100/ERPF. To calculate the FF, the MAG-3 ERPF values were converted to equivalent para-aminohippurate (PAH) ERPF values using the following formula: clearance of MAG-3 = 0.53 × clearance of PAH (23).

Glomerular capillary pressure (P_{GC}) was estimated indirectly from the pressure-natriuresis relationship by the method of Kimura et al. (24), based on mean arterial blood pressure, total plasma protein, and the FF.

Urine collection

Completeness of urine collections was verified from measurements of urinary creatinine. For each patient, data from 24-h urine collections were accepted if creatinine excretion fell within 2 SDs of the average creatinine excretion for that patient during the entire study period. On the 6 of 198 occasions when creatinine excretion fell outside this range, data for sodium, potassium, and urea were corrected for the mean creatinine excretion in that particular patient.

Statistical analysis

Data are presented as means ± SEM with 95% confidence intervals (CIs). Because some parameters, including PRA, ANG-II, and ACR were positively skewed, data were analyzed after logarithmic transformation and are shown as geometric mean multiplied/divided by the tolerance factor. Data measured at multiple time points were analyzed by a single-factor ANOVA with repeated measures, followed by Fisher's least significant difference test for multiple comparisons. Differences between two groups were analyzed using either Student's paired or unpaired *t* test or the χ^2 analysis for proportions, where appropriate. These analyses were performed using Statview V (Brainpower, Calabasas, CA). The effect of a low-sodium diet on a specific parameter (mean difference and 95% CI) was calculated as the difference between $losartan_{RS}$ and $losartan_{LS}$ or $placebo_{RS}$ and $placebo_{LS}$ for the losartan and placebo groups, respectively. No order effect was found. All analyses were performed according to the intention-to-treat approach.

RESULTS

Baseline characteristics

There were no significant baseline differences in mean arterial blood pressure, urinary sodium excretion, AER, BMI, duration of diabetes, HbA_{1c}, or pharmacotherapy for diabetes between the losartan and placebo groups (Table 1).

Sodium restriction

A similar degree of sodium restriction, as measured by 24-h urinary sodium excretion, was achieved in the $losartan_{LS}$ (85 ± 14 mmol/day) and $placebo_{LS}$ (80 ± 22 mmol/day; NS) study groups (Table 2). A change in weight (Δ weight) was observed during both the $losartan_{LS}$ (Δ weight: −1.9 ± 0.5 kg) and $placebo_{LS}$ (Δ weight: −1.0 ± 0.4 kg) phases, which was statistically significant when compared to the Δ weight recorded during the $losartan_{RS}$ (Δ weight: −0.1 ± 0.2 kg; $P = 0.006$) and $placebo_{RS}$ (Δ weight: 0.0 ± 0.2 kg; $P = 0.05$) phases.

Table 1—*Baseline characteristics of study patients*

Baseline characteristics	Losartan group	Placebo group
n	10	10
Sex (M/F)	10/0	9/1
Age (years)	60.6 ± 3.7	63.1 ± 3.9
Duration of diabetes (years)*	8.5 (1–38)	4.0 (1–10)
BMI (kg/m^2)	30.4 ± 2.1	28.1 ± 1.6
Serum creatinine (mmol/l)	97 ± 6.5	92 ± 2.7
24-h urine sodium (mmol/24hr)	230 ± 36	210 ± 26
Clinic mean arterial blood pressure (mmHg)	114 ± 3	111 ± 3
AER (μg/min)†	26.6 ± 1.4	32.6 ± 1.3
HbA_{1c} (%)	7.9 ± 0.5	7.4 ± 0.4
Diabetes treatment		
Diet alone	1	1
Metformin ± sulphonylurea	7	6
Thiazolidinedione	0	0
Insulin	2	3

Data are *n* or means ± SEM, except where otherwise noted. *Diabetes duration median (range); †AER geometric mean (tolerance factor)

Table 2—*Biochemical and RAS parameters in losartan and placebo groups*

	Losartan				Placebo			
	Week 0	Week 2	Week 4	ANOVA	Week 0	Week 2	Week 4	ANOVA
Urinary sodium excretion								
Regular-sodium diet	255 ± 33	222 ± 23	208 ± 20	NS	208 ± 15	207 ± 27	204 ± 27	NS
Low-sodium diet	225 ± 24	226 ± 25	85 ± 14†§	<0.0001	205 ± 29	163 ± 17	80 ± 22†§	0.0007
Fasting plasma glucose (mmol/l)								
Regular-sodium diet	10.5 ± 1.3	9.8 ± 1.2	9.3 ± 1.2	NS	9.8 ± 1.4	10.7 ± 1.2	9.6 ± 1.4	NS
Low-sodium diet	9.1 ± 0.7	8.9 ± 0.7	7.7 ± 0.6*	0.046	9.8 ± 0.7	9.1 ± 0.7	8.5 ± 1.5	NS
PRA (ng · ml^{-1} · h^{-1})								
Regular-sodium diet	0.47 (1.28)	1.31 (1.63)†	1.09 (1.52)†	0.0004	0.49 (1.31)	0.51 (1.27)	0.43 (1.27)	NS
Low-sodium diet	0.57 (1.29)	0.99 (1.46)	3.07 (1.63)†§	<0.0001	0.57 (1.31)	0.57 (1.3)	0.92 (1.3)†‡	<0.01
Plasma ANG-II (pg/ml)								
Regular-sodium diet	4.51 (1.24)	8.25 (1.41)†	10.04 (1.41)†	0.001	6.84 (1.29)	5.82 (1.25)	6.49 (1.21)	NS
Low-sodium diet	5.65 (1.29)	9.16 (1.4)	24.71 (1.53)†§	0.0002	6.06 (1.19)	6.65 (1.37)	10.8 (1.16)*‡	0.02
Plasma aldosterone (pmol/l)								
Regular-sodium diet	188.1 ± 33.3	273 ± 76.7	190.8 ± 38.7	NS	200.7 ± 43.2	233.4 ± 52.5	208.4 ± 31.4	NS
Low-sodium diet	209 ± 32.3	166.9 ± 34.5	345.3 ± 51.5†§	0.0009	173.9 ± 36.8	192 ± 34.5	401 ± 53.4†§	<0.0001

Data for PRA and ANG-II are geometric means (tolerance factor); data for urinary sodium excretion, fasting plasma glucose, and aldosterone are expressed as means ± SEM. *$P < 0.05$ vs. week 0; †$P < 0.01$ vs. week 0; ‡$P < 0.05$ vs. week 2; §$P < 0.01$ vs. week 2.

RAS activation

Measurements of parameters of the RAS over the study period are shown in Table 2. An increase in both PRA and plasma ANG-II levels was observed during the 2-week losartan run-in phase. During the losartan$_{RS}$ phase, there was no additional change in the plasma ANG-II level or PRA (week 4 vs. week 2: NS), but both indexes remained elevated when compared with baseline (week 4 vs. week 0: $P < 0.01$). During the losartan$_{LS}$ phase, there was a highly significant further increase in both the PRA (week 4 vs. week 2: $P < 0.01$) and plasma ANG-II level (week 4 vs. week 2: $P < 0.01$). No significant changes in either PRA or plasma ANG-II levels were observed during the placebo$_{RS}$ phase. However, during the placebo$_{LS}$ phase, there was a significant increase in both PRA (week 4 vs. week 2: $P < 0.01$) and plasma ANG-II levels (week 4 vs. week 2: $P < 0.05$). The absolute increase in mean PRA, but not in plasma ANG-II levels, was greater in the losartan$_{LS}$ than in the placebo$_{LS}$ group (PRA: 3.07 ± 1.63 vs. 0.92 ± 1.3 ng · ml^{-1} · h^{-1}, respectively, P =

Table 3—*Hemodynamic and renal parameters during placebo$_{RS}$ and placebo$_{LS}$*

	Placebo$_{RS}$			Placebo$_{LS}$			Δ Placebo$_{LS}$ − Δ placebo$_{RS}$	
Parameter	Week 2	Week 4	Δ Week 4–2	Week 2	Week 4	Δ Week 4–2	Δ	*P*
Blood pressure (mmHg)								
24-h								
Systolic	138.6 ± 4.2	137.5 ± 4.0	−1.1 ± 2.1	131.9 ± 4.5	132.6 ± 4.6	0.7 ± 2.7	1.8 (−5.9 to 9.5)	NS
Diastolic	81.9 ± 3.1	80.9 ± 2.7	−1 ± 1.1	77.3 ± 1.9	79.6 ± 2.7	2.3 ± 1.9	3.3 (−1.7 to 8.3)	NS
Mean arterial pressure	100.8 ± 2.9	100.4 ± 2.8	−0.4 ± 1.5	97.5 ± 2.9	97.0 ± 2.8	−0.5 ± 2.0	−0.1 (−5.9 to 5.7)	NS
Awake								
Systolic	141.8 ± 4.4	141.5 ± 4.1	−0.3 ± 2.4	135.1 ± 4.7	135.1 ± 4.8	0 ± 2.7	0.3 (−7.9 to 8.5)	NS
Diastolic	84.2 ± 3.3	83.4 ± 2.7	−0.8 ± 1.3	82.3 ± 3.0	81.7 ± 2.9	−0.6 ± 1.8	0.2 (−4.6 to 5.0)	NS
Mean arterial pressure	103.2 ± 3.2	103.1 ± 2.9	−0.1 ± 1.8	100.3 ± 3.0	98.9 ± 3.1	−1.4 ± 2.2	−1.3 (−7.7 to 5.1)	NS
Sleep								
Systolic	124.8 ± 4.1	122.2 ± 3.6	−2.6 ± 2.4	121.0 ± 4.1	122.4 ± 3.8	1.4 ± 3.0	4.0 (−3.7 to 11.7)	NS
Diastolic	72.4 ± 3.3	71.4 ± 2.4	−1.0 ± 1.7	67.8 ± 1.9	72.1 ± 2.9	4.3 ± 2.5	5.3 (−2.0 to 12.6)	NS
Mean arterial pressure	93.3 ± 3.1	89.7 ± 2.5	−1.6 ± 1.4	88.1 ± 2.5	89.4 ± 2.5	1.3 ± 2.1	2.9 (−3.3 to 9.1)	NS
GFR (ml · min^{-1} · 1.73 m^{-2})	100.7 ± 5.4	100.5 ± 4.0	−0.2 ± 2.1	99.0 ± 4.7	95.0 ± 4.6	−4.0 ± 2.0	−3.8 (−9.4 to 1.9)	NS
MAG-3 ERPF (ml · min^{-1} · 1.73 m^{-2})	270.7 ± 20.8	276.3 ± 19.1	5.6 ± 14.9	267.7 ± 21.5	272.0 ± 20.2	4.3 ± 15	−1.3 (−53 to 50)	NS
FF (%)	20.3 ± 1.2	19.7 ± 0.8	−0.6 ± 1.2	20.2 ± 1.1	18.9 ± 0.7	−1.3 ± 1.0	−0.8 (−4.7 to 3.1)	NS
P_{GC} (mmHg)	42.5 ± 2.6	41.0 ± 3.7	−1.5 ± 2.0	39.0 ± 2.9	36.4 ± 3.3	−2.5 ± 2.5	−1.0 (−7.8 to 5.7)	NS

Data means ± SEM or mean difference (95% CI).

Table 4—*Hemodynamic and renal parameters during losartan$_{RS}$ and losartan$_{LS}$*

Parameter	Losartan$_{RS}$ Week 2	Losartan$_{RS}$ Week 4	Losartan$_{RS}$ Δ Week 4–2	Losartan$_{LS}$ Week 2	Losartan$_{LS}$ Week 4	Losartan$_{LS}$ ΔWeek 4–2	Δ Losartan$_{LS}$ − Δ losartan$_{RS}$ Δ	*P*
Blood pressure (mmHg)								
24-h								
Systolic	139.6 ± 3.9	139.6 ± 4.8	0 ± 2.1	141.4 ± 4.0	131.7 ± 3.5	−9.7 ± 2.7	−9.7 (−17.2 to −2.2)	0.002
Diastolic	77.8 ± 1.5	78.2 ± 1.8	0.4 ± 0.9	78.9 ± 1.2	73.8 ± 1.8	−5.1 ± 1.4	−5.5 (−8.4 to −2.6)	0.002
Mean arterial pressure	99.3 ± 1.9	98.9 ± 2.4	−0.4 ± 1.5	100.6 ± 1.8	92.9 ± 1.9	−7.7 ± 1.7	−7.3 (−11.3 to −3.3)	0.003
Awake								
Systolic	142.5 ± 4	142.1 ± 4.9	−0.4 ± 2.2	143.5 ± 4.5	133.6 ± 4.0	−9.9 ± 3.2	−9.5 (−18.4 to −0.6)	0.039
Diastolic	80.2 ± 1.6	80.1 ± 1.8	−0.1 ± 0.8	80.7 ± 1.4	75.3 ± 2.0	−5.4 ± 1.8	−5.3 (−9.3 to −1.3)	0.015
Mean arterial pressure	101.8 ± 2.1	100.5 ± 2.3	−1.3 ± 1.4	101.1 ± 2.7	94.1 ± 2.4	−7.0 ± 2.6	−5.7 (−11.3 to −0.1)	0.048
Sleep								
Systolic	129.9 ± 3.4	129.6 ± 5.3	−0.3 ± 2.3	134.2 ± 3.7	123.8 ± 3.1	−10.4 ± 3.2	−10.1 (−19.7 to −0.5)	0.041
Diastolic	70.3 ± 2.1	70.3 ± 2.2	0 ± 1.8	72.5 ± 1.7	67.7 ± 2.2	−4.8 ± 1.5	−4.8 (−11.2 to 1.5)	0.12
Mean arterial pressure	91.4 ± 1.8	91.1 ± 2.9	−0.3 ± 1.9	94.8 ± 1.6	88.2 ± 1.6	−6.6 ± 2.0	−6.3 (−12.8 to 0.8)	0.065
GFR (ml · min^{-1} · 1.73m^{-2})	101.1 ± 6.1	98.8 ± 6.3	−2.3 ± 2.1	96.9 ± 6.7	91.9 ± 5.9	−5.0 ± 1.7	−2.7 (−8.1 to 2.6)	0.28
MAG-3 ERPF (ml · min^{-1} · 1.73 m^{-2})	272.9 ± 21.8	267.3 ± 23.4	−5.6 ± 9.9	275.5 ± 20.9	269.2 ± 19.6	−6.3 ± 9.3	−0.7 (−26 to 25)	0.95
FF (%)	20.1 ± 1.0	20.2 ± 1.3	0.2 ± 1.0	18.8 ± 0.8	18.2 ± 0.6	−0.6 ± 0.4	−0.7 (−3.3 to 1.8)	0.53
P_{GC} (mmHg)	53.3 ± 3.8	51.9 ± 3.6	−1.4 ± 1.7	54.4 ± 3.9	45.4 ± 4.4	−9.0 ± 1.7	−7.6 (−11.8 to −3.5)	0.002

Data expressed as means ± SEM or mean difference (95% CI).

0.048; plasma ANG-II: 24.71 ± 1.53 vs. 10.8 ± 1.16 pg/ml, respectively, $P = 0.09$). A significant increase in plasma aldosterone was observed during both the losartan$_{LS}$ (week 4 vs. week 2: $P < 0.01$) and placebo$_{LS}$ (week 4 vs. week 2: $P < 0.01$) phases. No significant change in plasma aldosterone was observed during the losartan 2-week run-in phase or during the losartan$_{RS}$ or placebo$_{RS}$ phase.

Ambulatory blood pressure

ABP fell significantly during the losartan$_{LS}$ phase, but remained unchanged during the placebo$_{LS}$ phase (Tables 3 and 4). The change in blood pressure was greater in the losartan$_{LS}$ compared with the losartan$_{RS}$ phase: the mean difference between the losartan$_{LS}$ and losartan$_{RS}$ phases for 24-h systolic, diastolic, and mean arterial blood pressures was –9.7 mmHg (CI −17.2 to –2.2), −5.5 mmHg (−8.4 to –2.6), and –7.3 mmHg (−11.3 to –3.3), respectively.

When 24-h ABP was analyzed by wake/sleep periods, there were significant decreases in blood pressure during the losartan$_{LS}$ phase in wake systolic, diastolic, and mean arterial pressure and in sleep systolic blood pressure.

Changes in ABP from baseline were assessed in a subset of 12 patients. Figure 2 shows that the antihypertensive effect of losartan was doubled by the addition of a low-sodium diet. In the losartan group ($n = 6$), after the 2-week run-in period with losartan therapy on a regular-sodium diet, the change in ABP was –5.2 ± 3.6 mmHg (NS) from baseline. After 2 weeks of low-sodium diet, from week 2 to week 4, the change from baseline was –10.7 ± 3.7 mmHg (weeks 0−2 vs. weeks 0−4: $P = 0.02$). In the placebo group ($n = 6$), no significant changes in 24-h ABP from baseline were observed at week 2 or after 2 weeks of a low-sodium diet at week 4 (−0.3 ± 1.2 and −0.5 ± 2.8 mmHg, respectively; NS).

ACR

In the losartan group, there was a significant reduction in the ACR in the low-sodium phase that was not observed in the regular-sodium phase: losartan$_{LS}$ −29% (CI −50 to –8.5%) vs. losartan$_{RS}$ +14% (−19.4 to 47.9%) ($P = 0.02$). In the placebo group, there was no significant change in ACR in either the low- or the regular-sodium phase: placebo$_{LS}$ +25% (CI −39.3 to 89.3%) vs. placebo$_{RS}$ –13.5% (−41.1 to 14.0%) ($P = 0.2$).

In the losartan group, ACR did not decrease significantly from baseline until a low-sodium diet was added (Fig. 3).

In the losartan group, when the mean percent difference in ACR between low- and regular-sodium diets (losartan$_{LS}$ − losartan$_{RS}$) was compared with the same parameter in the placebo

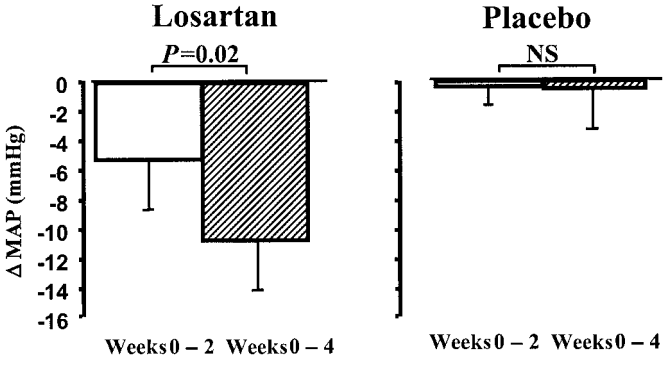

Figure 2—*Change in mean arterial blood pressure (MAP) from baseline in losartan and placebo groups during run-in (□) and low-sodium (▨) phases.*

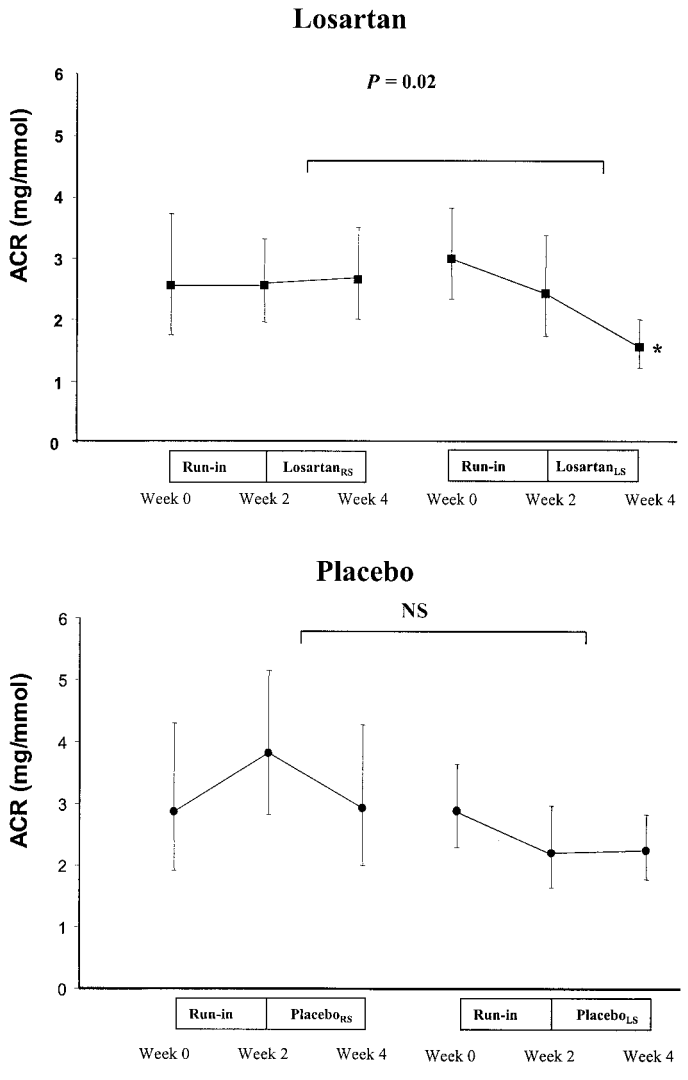

Figure 3—*ACR in losartan and placebo groups over study period. Data are geometric mean (tolerance factor).* *P < *0.01 vs. weeks 2 and 0.*

group (placebo$_{LS}$ − placebo$_{RS}$), a significantly greater albuminuria-lowering effect of the low-sodium diet was found in the losartan group: losartan −43.5% (CI −77.5 to −9.6%) vs. placebo +38.5% (−31.7 to 108.8%) (P = 0.03).

Renal hemodynamics

No significant changes in GFR, ERPF, or FF were observed during losartan$_{LS}$ or placebo$_{LS}$ phases (Tables 3 and 4). A significant change in calculated P_{GC} was found in the losartan$_{LS}$ phase (−9.0 ± 1.7 mmHg) compared with the losartan$_{RS}$ phase (−1.4 ± 1.7 mmHg) (P = 0.002). No changes in P_{GC} were found in the placebo group.

Plasma and urinary electrolytes, urea, and creatinine

During the period of dietary sodium restriction, there were no significant changes in plasma concentrations of sodium, urea, or creatinine, and also no significant changes in the urinary excretion of potassium, urea, and creatinine (data not shown).

At the beginning of each phase, HbA_{1c} was measured. No differences in glycemic control between phases was found for losartan (7.7 ± 0.5 vs. 7.5 ± 0.3% for losartan$_{RS}$ vs. losartan$_{LS}$, respectively; NS) or placebo (7.3 ± 0.3 vs. 7.3 ± 0.3% for placebo$_{RS}$ vs. placebo$_{LS}$, respectively; NS). In the losartan$_{LS}$ group, there was a small but significant decrease in fasting blood glucose, of dubious clinical significance, at week 4 (Table 2).

Correlations

In both groups, significant correlations were observed between the percent reduction in 24-h urinary sodium excretion and the fall in mean arterial blood pressure (losartan$_{LS}$: y = 0.22x + 5.55, r = 0.68, P = 0.03; placebo$_{LS}$: y = 0.11x + 4.95, r = 0.64, P = 0.05) (Fig. 4*A* and *B*). The 95% CI (−0.11 to 0.33) for the difference between the gradients (0.11) showed there was no significant difference between the regression lines.

In the losartan group, a strong and significant correlation was found between the fall in mean arterial blood pressure and the percent reduction in ACR (y = 5.96x + 0.00, r = 0.70, P = 0.02) (Fig. 5). No significant correlations between the fall in P_{GC} and percent reduction in ACR or between changes in mean arterial pressure and ERPF were detected.

CONCLUSIONS — This study demonstrated the important role that dietary sodium plays in modulating the antihypertensive and antiproteinuric effects of ANG-receptor antagonists in type 2 diabetes. In patients taking losartan, the magnitude of blood pressure reduction that occurred after 2 weeks of low-sodium diet was equivalent to the effects of adding a second antihypertensive agent (25) and led to an approximate doubling of the antihypertensive effect of the drug.

Unlike many studies that have examined the effects of a low-sodium diet, the current study was performed on an ambulatory basis and without pre-prepared diets. Patient dietary education focused on identifying the sodium content of common foods and determining sodium content by reading food labels. This approach was able to achieve significant reductions in mean urinary sodium excretion, to 80−85 mmol/24 h, and was associated with activation of the systemic RAS. Effects of sodium restriction in hypertensive and nonhypertensive subjects to <100 mmol/day have been recently studied by the Dietary Approaches to Stop Hypertension investigators, who found greater blood pressure reductions during sodium restriction from 100 to 60 mmol/day compared with a reduction from 150 to 100 mmol/day (26). The efficacy of dietary sodium reduction on lowering blood pressure in diabetic subjects has not been extensively character-

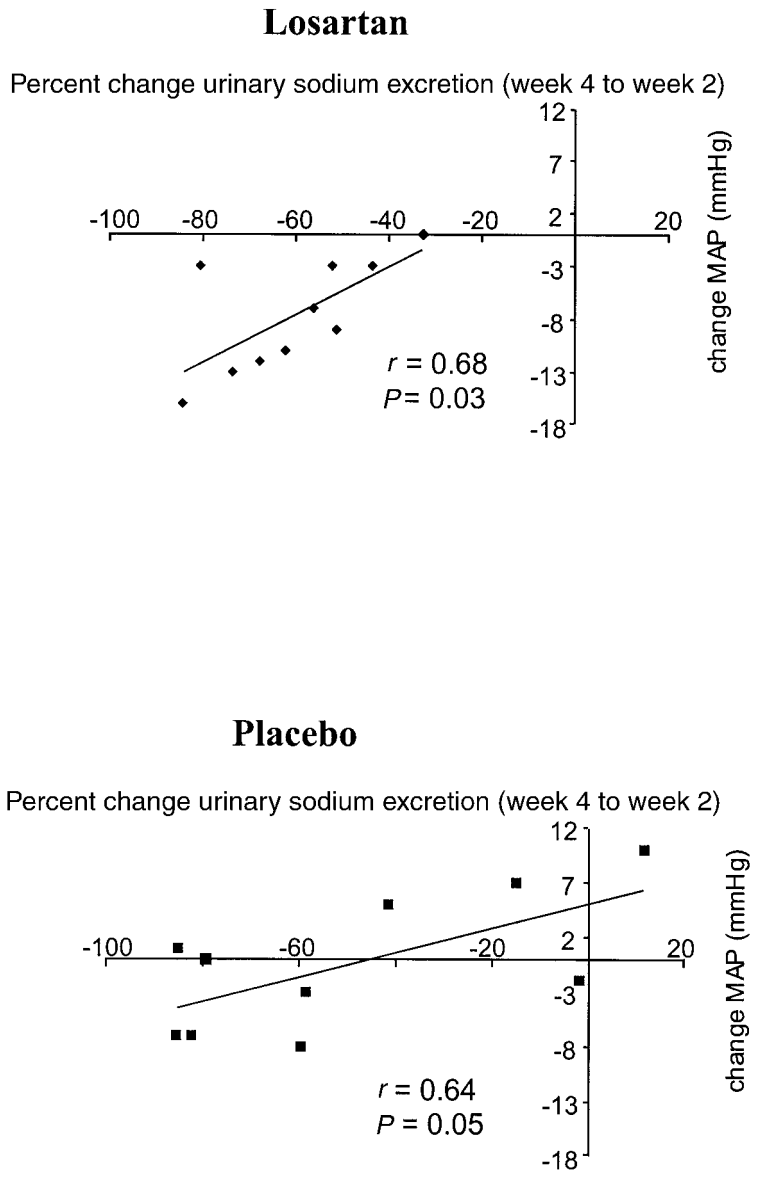

Figure 4—*Percent change in urinary sodium excretion versus change in mean arterial pressure for losartan (*A*) and placebo (*B*) groups*

ized. Similar to the findings in the present study, one previous randomized study in type 2 diabetes showed significant blood pressure−lowering effects of sodium restriction; however, unlike in the present study, subjects in that study had more severe hypertension (>160/90 mmHg) and some were on concomitant antihypertensive therapy (27). It remains to be determined whether increased exchangeable body sodium and sodium retention alters the magnitude and temporal nature of the responsiveness to dietary sodium restriction. In the present study, the degree of reduction in urinary sodium excretion was correlated to a reduction in mean arterial blood pressure in both the losartan and placebo groups (Fig. 4*A* and *B*), with a nonsignificant trend for greater effects of sodium restriction in the losartan group. The effects of losartan and low-sodium diet on plasma ANG-II, aldosterone, and PRA have been well characterized, and the present findings are consistent with those of previous studies (28–30).

Like previous studies, this study demonstrated that the antiproteinuric effects of losartan in diabetic patients is closely associated with reductions in blood pressure (31–33). However, in the present study, a significant decrease in both blood pressure and albuminuria was observed only when a low-sodium diet was added to losartan therapy.

The mechanism by which the addition of a low-sodium diet reduced albuminuria in the losartan group appears to be related to blood pressure reduction, with the fall in mean arterial blood pressure correlating with the percent reduction in ACR (Fig. 5). A significant correlation between decreases in albuminuria and blood pressure has been demonstrated by a meta-analysis for both ACE inhibitors and conventional antihypertensive therapy (34). To further determine whether changes in various renal parameters, including glomerular hemodynamics, may be involved, measurements of GFR, ERPF, FF, and calculated P_{GC} were performed. No significant changes in GFR, ERPF, or FF were observed with low-sodium diet in either group. A fall in calculated P_{GC}, which occurred with a low-sodium diet in the losartan group, was linked to a decrease in albuminuria. The elegant micropuncture studies performed by Zatz et al. (35) in diabetic rodents have previously suggested a pivotal role for raised intraglomerular pressure in mediating albuminuria. In those studies, the increase in intraglomerular pressure was reduced by blockade of the RAS with an ACE inhibitor, and this was associated with attenuation of albuminuria. Although P_{GC} was only calculated and is therefore an indirect measurement of intraglomerular pressure, the findings in the present study are consistent with the hypothesis that a reduction in P_{GC} is closely linked to a reduction in albuminuria.

Other potential confounding factors that could influence GFR or albuminuria, such as changes in glycemic control (36) or protein intake (37), were also evaluated. No change in dietary protein intake, as assessed by urinary urea excretion, was observed during the period of low-sodium diet, nor were there clinically significant changes in overall glycemic control, as assessed by fasting blood glucose and HbA_{1c}.

Because ANG-II has both hemodynamic and trophic effects, blockade of its receptors may potentially exert effects on albuminuria reduction via nonhemodynamic mechanisms. In a meta-analysis, ACE inhibitors were found to exert specific antiproteinuric effects, with minimal changes in blood pressure (34). In this study, however, no reduction in albumin-

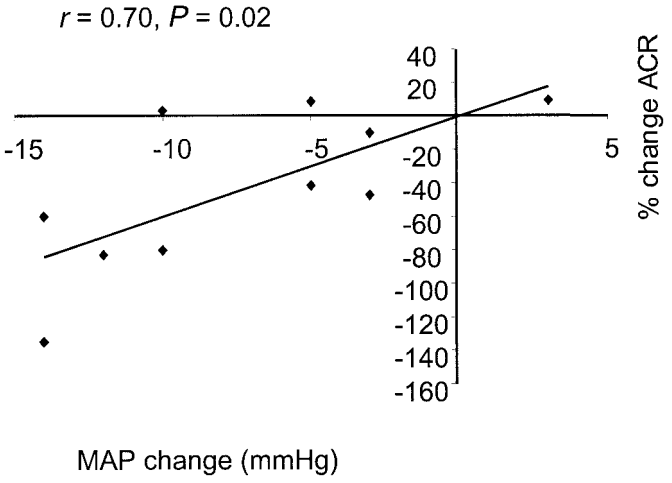

Figure 5—*Change in mean arterial blood pressure versus percent change ACR in losartan group*

uria was observed after 4 weeks of losartan therapy while patients remained on a regular-sodium diet, during which urinary sodium excretion was >200 mmol/day. This finding is consistent with the previous observation in streptozotocin-induced diabetic rats that a high-salt diet blocks the antihypertensive and antiproteinuric effects of ACE inhibitors (10).

This study does not support the concept of sodium modulation of proteinuria, independent of blood pressure reduction, that has been previously described in type 2 diabetic patients receiving verapamil (38).

The observation that renal plasma flow did not change between the regular- and low-sodium diets in the placebo group is consistent with a blunted vasodilator renal plasma flow response to a high-sodium diet, which has been previously described in patients with type 2 diabetes (17) and essential hypertension (30,39). In a previous study of the effects of low and high dietary sodium on mean arterial blood pressure and renal hemodynamics in essential hypertension, a rise in blood pressure on a high-sodium diet was associated with a blunted increase in ERPF (30). In our study, no correlation between the changes in mean arterial blood pressure and ERPF was found.

This study demonstrated that a low-sodium diet optimizes the renoprotective effects of the ANG-receptor blocker, losartan. It also showed that a low-sodium diet is achievable on an ambulatory basis in the short term. Combination antihypertensive medication in a single tablet, consisting of a thiazide diuretic and an ACE inhibitor or ANG-receptor antagonist, has recently become widely available. Moderate sodium restriction, as achieved in the present study, has been shown to be as effective as a thiazide diuretic in lowering blood pressure in the presence of an ACE inhibitor in essential hypertension (40). However, a low-sodium diet is a preferred option because, unlike diuretic therapy, it is not associated with potential adverse effects on lipid and glucose metabolism, nor is it associated with potential disturbances of serum potassium and sodium levels (41). We propose that a low-sodium diet (<100 mmol/day) be used in subjects with type 2 diabetes who are receiving monotherapy with an ANG-receptor antagonist when further blood pressure reduction is required. In these circumstances, the addition of a low-sodium diet should be considered as an appropriate alternative to additional pharmacological antihypertensive agents, including combination therapy with a diuretic.

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