European Journal of Clinical Nutrition (2012) **66**, 1214–1218

www.nature.com/ejcn

ORIGINAL ARTICLE

Dietary salt intake is related to inflammation and albuminuria in primary hypertensive patients

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BACKGROUND/OBJECTIVES: In this study, we hypothesized that dietary salt intake may be related with inflammation and albuminuria independently from blood pressure (BP) in non-diabetic hypertensive patients.
SUBJECTS/METHODS: A total of 224 patients with primary hypertension were included in the study. Serum C-reactive protein (CRP) levels, 24-h urine sodium and albumin excretion were measured in all patients. The subjects were divided into tertiles according to the level of 24-h urinary sodium excretion: low-salt-intake group ($n = 76$, mean urine sodium: 111.7 ± 29.1 mmol/24 h), medium-salt-intake group ($n = 77$, mean urine sodium: 166.1 ± 16.3 mmol/24 h) and high-salt-intake group ($n = 71$, mean urine sodium: 263.6 ± 68.3 mmol/24 h).
RESULTS: Systolic and diastolic BP measurements of patients were similar in the three salt-intake groups. CRP and urinary albumin levels were significantly higher in high-salt-intake group compared with medium- and low-salt-intake groups ($P = 0.0003$ and $P = 0.001$, respectively). CRP was positively correlated with 24-h urinary sodium excretion ($r = 0.28$, $P = 0.0008$) and albuminuria, whereas albuminuria was positively correlated with 24-h urinary sodium excretion ($r = 0.21$, $P = 0.0002$). Multiple regression analysis revealed that urinary sodium excretion was an independent predictor of both CRP and albuminuria.
CONCLUSIONS: These findings suggest that high salt intake is associated with enhanced inflammation and target organ damage reflected by increased albuminuria in treated hypertensive patients independent of any BP effect.

European Journal of Clinical Nutrition (2012) **66,** 1214–1218; doi:10.1038/ejcn.2012.110; published online 22 August 2012

Keywords: albuminuria; hypertension; inflammation; salt intake

INTRODUCTION

Salt intake is an important factor in the genesis of primary hypertension. Epidemiological and clinical data have showed that high salt intake is associated with increased risk of cardiovascular diseases and stroke.[1] Recent work has provided further evidence that high dietary salt intake may even partly cause blood pressure (BP) -independent target organ damage including left ventricular hypertrophy and microalbuminuria.[2–4] Microalbuminuria is a significant predictor of endothelial dysfunction and an independent marker of cardiovascular diseases in patients with primary hypertension.[5,6] Several studies have demonstrated that high salt intake is positively related to urinary albumin excretion and this relation may be independent of BP.[3,4,7] The mechanisms responsible for this effect are unclear. In animal models, dietary salt overload has been demonstrated to contribute to renal injury documented by albuminuria and decreased glomerular filtration rate with a minimally increased arterial pressure.[8,9] Inflammatory mechanisms have been proposed to have a role in this nephrotoxic effect of salt excess.[9–13] The role of inflammation in the initiation and progression of cardiovascular diseases is increasingly recognized.[14,15] Studies in hypertensive individuals have shown increased plasma and vascular tissue levels of C-reactive protein (CRP) and several inflammatory cytokines, suggesting a potential association between vascular inflammation and hypertension.[16–19]

Although the evidence for a direct relationship between salt intake and BP is basically established,[20–23] the clinical evidence is not adequate to consider whether this effect translates into increased incidence of cardiovascular diseases independent from BP in patients with high dietary salt consumption. In this study, we hypothesized that dietary salt intake may be related with inflammation and albuminuria independently from BP in non-diabetic hypertensive patients.

MATERIALS AND METHODS

Study population

A total of 289 patients who had been previously diagnosed as primary hypertension and who were under anti-hypertensive treatment at least 3 months were recruited from patients presenting to our outpatient nephrology clinic for follow-up treatment of primary hypertension within a period of 12 months. From the 289 patients, we excluded 65 patients meeting at least one of the following criteria: patients with diabetes mellitus or coronary heart disease ($n = 26$), chronic inflammatory diseases ($n = 3$), glomerular filtration rate < 60 ml/min/1.73 m^2 ($n = 12$), urine albumin greater than 300 mg/day ($n = 10$) and patients on diuretic therapy ($n = 14$). Therefore, 224 non-diabetic hypertensive patients were enrolled in this study.

Demographic findings of all patients including age, gender, smoking status, number and class of anti-hypertensive drugs currently used were recorded. All patients underwent BP and anthropometric measurements (height in cm, body weight in kg), and venous blood drawing. Twenty-four hour urine was collected from all participants for measurement of sodium and albumin excretion. To verify a correct urine sampling, 24-h urinary creatinine excretion was measured. Office BP was measured using a mercury sphygmomanometer after at least 15 min of rest in the sitting position. Patients were asked to remove all clothing that covers the location of cuff and were comfortably seated, with the legs uncrossed and

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Received 20 April 2012; revised 24 July 2012; accepted 25 July 2012; published online 22 August 2012

the back and arm supported, such that the middle of the cuff on the upper arm was at the level of the right atrium. Cuff width was selected according to subject's arm circumference. The cuff was inflated to at least 30 mm Hg above the point at which the radial pulse disappeared. The mercury column was deflated at 2–3 mm/s, and the first and last audible sounds were taken as systolic and diastolic BP. A minimum of two readings were taken at intervals of at least 1 min, and the average of these readings were used to represent the patient's BP. If there was >5 mm Hg difference between the first and second readings, additional one or two readings were obtained, and then the average of these multiple readings was considered for the analysis. Venous blood samples were obtained after an overnight fast for the estimation of fasting glucose, lipid levels (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides), albumin, blood urea nitrogen, creatinine, complete blood count, erythrocyte sedimentation rate and CRP. Serum lipids were determined by using an autoanalyzer (Hitachi P800, Holliston, MA, USA). CRP was detected by rate nephelometry (IMMAGE Immunochemistry System, Beckerman Coulter, Inc., Fullerton, CA, USA). The CRP detection range corresponded to concentrations of 0.01–9.6 mg/dl (normal values <0.8 mg/dl). Urinary albumin was measured by immunonephelometry (Dade Behring Diagnostics, Marburg, Germany) with a lower limit of detection of 2.3 mg/l. The intra- and interassay CVs were 2.7% and 4.5%, respectively. Other biochemical variables were analyzed using standard laboratory techniques for hospital use.

At the end of the measurements, the subjects were divided into tertiles according to the level of 24-h urinary sodium excretion: low-salt-intake group ($n=76$, mean urinary sodium excretion: 111.7 ± 29.1 mmol/24 h), medium-salt-intake group ($n=77$, mean urinary sodium excretion: 166.1 ± 16.3 mmol/24 h) and high-salt-intake group ($n=71$, mean urinary sodium excretion: 263.6 ± 68.3 mmol/24 h). The study protocol was approved by ethics committee of Hacettepe University, an institutional ethics committee. Informed consent was taken from all the participants.

Statistical analysis

Distribution of the variables was checked using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were presented as mean ± s.d. Variables with unequal distribution were expressed as median and interquartile ranges (Q1–Q3). Categorical variables were presented as numbers and percentages. To determine the presence of any difference between groups, if data were normally distributed and variances were homogeneous, one-way ANOVA was used, otherwise analyses were done with Kruskal–Wallis test. To determine the groups between which there was a statistically significant difference, Tukey's HSD test was used, if the parametric test conditions were satisfied, and Mann–Whitney *U* test was used after Bonferoni correction, if the parametric test conditions were not satisfied. Categorical variables were compared with χ^2 or Fischer's exact test. Spearman's correlation coefficients was calculated to evaluate the relationship between continous variables. Linear regression analysis was introduced so as to determine the independent associations of CRP and albuminuria. Statistical significance was considered at a two-tailed value of $P<0.05$. Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 13.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and biochemical characteristics of patients

Clinical and biochemical characteristics of the patients are shown in the Table 1. No differences were observed in terms of gender distribution, age, body mass index (BMI), smoking status, duration of hypertension, types of anti-hypertensive agents and laboratory findings between the low-, medium- and high-salt-intake groups.

Blood pressure measurements

Systolic and diastolic BP values of patients were similar despite the increasing levels of 24-h urinary sodium excretion in the study groups. To investigate whether the dose of anti-hypertensive therapy was a factor for similar BP values in the tertile groups, we also determined the number and types of anti-hypertensive drugs in the groups. Although the types of the drugs were similar between the groups, the mean number of anti-hypertensive drugs

Table 1. Demographic and biochemical characteristics of low-, medium- and high-salt-intake groups[a]

Parameter	*Low-salt-intake group* (n = *76*)	*Medium-salt-intake group* (n = *77*)	*High-salt-intake group* (n = *71*)	P-*value*
Male, *n* (%)	46 (61)	50 (65)	41 (58)	0.67
Age (years)	51.8 ± 13.1	51.9 ± 10.2	52.8 ± 11.2	0.85
BMI (kg/m^2)	28.4 ± 4.7	28.2 ± 4.1	29.2 ± 5.1	0.16
Current smokers (%)	25	22	26	0.66
Duration of hypertension (months)	45.6 ± 31.3	44.6 ± 32.6	46.2 ± 39.6	0.58
No. of anti-hypertensive drugs	1.22 ± 0.41	1.24 ± 0.43	1.45 ± 0.50	0.004[b]
Antihpertensive therapy, (n)				
ACE inhibitor	23	26	27	0.80
Angiotensin II receptor blocker	18	19	19	0.72
Ca channel blocker	31	27	32	0.75
Beta blocker	17	19	22	0.66
Alpha blocker	4	4	6	0.88
Mean systolic BP (mm Hg)	130.5 ± 15.1	130.8 ± 17.0	132.9 ± 13.1	0.83
Mean diastolic BP (mm Hg)	82.1 ± 10.5	85.8 ± 12	82.9 ± 9	0.39
Hemoglobin (g/dl)	13.1 ± 1.9	13.0 ± 1.7	13.3 ± 1.4	0.81
ESR (mm/h)	12.3 ± 8.6	13.0 ± 10.8	11.3 ± 7.4	0.77
Creatinine (mg/dl)	1.00 ± 0.35	0.99 ± 0.34	0.99 ± 0.32	0.62
BUN (mg/dl)	15.7 ± 6.2	16.5 ± 9.1	15.7 ± 5.6	0.12
Albumin (g/dl)	3.8 ± 0.4	3.9 ± 0.4	3.8 ± 0.5	0.58
Total cholesterol (mg/dl)	181 ± 36	186 ± 46	188 ± 37	0.42
LDL-cholesterol (mg/dl)	101 ± 35	104 ± 36	105 ± 33	0.55
HDL-cholesterol (mg/dl)	38 ± 13	38 ± 11	39 ± 10	0.66
Triglyceride (mg/dl)	187 ± 61	188 ± 59	190 ± 78	0.22
24-h urinary sodium (mmol/24 h)	111.7 ± 29.1	166.1 ± 16.3	263.6 ± 68.3	0.001[b]
Creatinine clearance (ml/min/1.73 m^2)	91 ± 24	90 ± 27	89 ± 28	0.56

Abbreviations: BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Continuous variables are reported as mean ± s.d. for normally distributed data. Categorical variables are reported as number (percentage). [b]One-factor ANOVA.

was significantly higher in high-salt-intake group compared with low- or medium-salt-intake groups ($P=0.003$ and $P=0.009$, respectively). However, the mean number of anti-hypertensive drugs did not differ between low- and medium-salt-intake groups ($P=0.73$; Table 1). To evaluate a possible association of 24-h urinary sodium excretion with BP measurements and number of anti-hypertensive drugs, we used bivariate correlation analysis. There were no significant correlations between 24-h urinary sodium excretion and systolic or diastolic BP ($P=0.16$ and $P=0.47$, respectively) in the whole study population, whereas 24-h urinary sodium excretion significantly correlated with the number of anti-hypertensive drugs ($r=0.17$, $P=0.008$).

Serum CRP and urinary albumin levels

Figure 1 shows CRP values as an inflammatory marker in low-, medium- and high-salt-intake groups. CRP was significantly higher in high-salt-intake group compared with medium- and low-salt-intake groups ($P=0.0003$). However, CRP levels did not differ between the low- and medium-salt-intake groups. Similarly, urinary albumin levels were higher in high-salt-intake group compared with medium- and low-salt-intake groups ($P=0.001$), whereas comparison of medium- and low-salt-intake groups revealed no difference (Figure 2). In correlation analysis, serum CRP levels were positively correlated with systolic BP ($r=0.24$, $P=0.031$), 24-h urinary sodium excretion ($r=0.28$, $P=0.0008$) and 24-h urinary albumin excretion ($r=0.43$, $P=0.0001$) in the whole study population. In a multiple regression analysis model, using CRP as the dependent variable, urinary sodium excretion and albuminuria were independent predictors of CRP ($\beta=0.28$, $P=0.004$ and $\beta=0.46$, $P=0.0005$, respectively; Table 2). In the total study population, the main correlates of urinary albumin excretion were 24-h urinary sodium excretion ($r=0.21$, $P=0.0002$), BMI ($r=0.38$, $P=0.02$) and serum creatinine level ($r=0.16$, $P=0.005$). A multiple regression analysis revealed that 24-h urinary sodium excretion and serum creatinine levels were independent predictors of albuminuria ($\beta=0.22$, $P=0.0001$ and $\beta=0.17$, $P=0.003$, respectively; Table 3). However, age, gender, smoking status, BMI, systolic and diastolic BP, and lipid levels did not correlate with albuminuria.

DISCUSSION

During the past decade, significant amount of data have indicated that high salt intake causes increased BP due to hypervolemia in short term and increased peripheral vascular resistance through the process of autoregulation in long term.[24,25] However, a clear relationship is not fully established, as the BP response to high salt intake is variable among individuals.[23] In the present study, although the BP levels did not differ between the groups with the increasing amount of salt intake from low- to high-salt-intake groups, we observed that the patients in the high-salt-intake group required more antihypertensive drugs than the low- and medium-salt-intake groups to maintain the similar BP levels. Furthermore, we demonstrated a significant correlation between

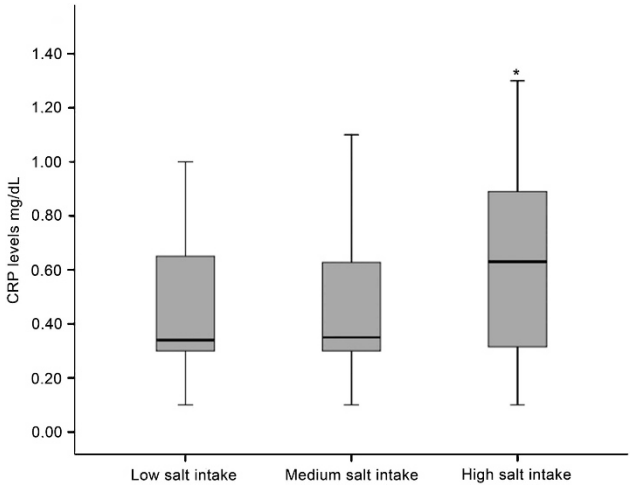

Figure 1. Median and distribution of serum CRP levels in low-, medium- and high-salt-intake groups. The bar in each box indicates the median value. Upper and lower borders of the boxes are the 25th and 75th percentiles, respectively. Maximum and minimum values are shown by the error bars (*$P=0.0003$).

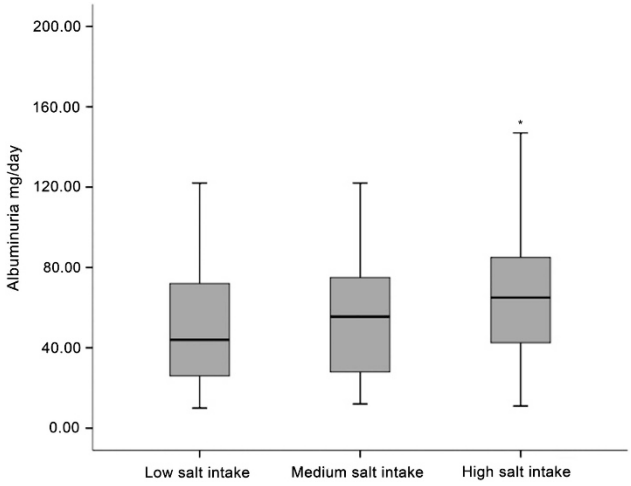

Figure 2. Median and distribution of urinary albumin levels in low-, medium- and high-salt-intake groups. The bar in each box indicates the median value. Upper and lower borders of the boxes are the 25th and 75th percentiles, respectively. Maximum and minimum values are shown by the error bars (*$P=0.001$).

Table 2. Correlation analysis of c-reactive protein with different variables (a) and multivariable linear regression analysis showing independent variables associated with serum c-reactive protein as the dependent variable in treated hypertensive patients (b)

a

Variables	r	P-*value*
Age	−0.16	0.75
Gender	−0.24	0.66
BMI	−0.06	0.20
Mean systolic BP	0.24	0.03
Mean diastolic BP	0.15	0.63
Creatinine	−0.85	0.71
Total cholesterol	0.12	0.18
LDL-cholesterol	0.14	0.22
HDL-cholesterol	0.22	0.33
Triglyceride	0.28	0.38
24-h urinary sodium excretion	0.18	0.0008
24-h urinary albumin excretion	0.26	0.0001

b

Variables	*Beta*	P-*value*
Mean systolic BP	0.15	0.21
24-h urinary sodium excretion	0.28	0.004
24-h urinary albumin excretion	0.46	0.0005

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. Correlation analysis of urinary albumin with different variables (a) and multivariable linear regression analysis showing independent variables associated with urinary albumin as the dependent variable in treated hypertensive patients (b)

a

Variables	r	P-*value*
Age	0.05	0.91
Gender	−0.33	0.54
BMI	0.38	0.02
Smoking status	0.14	0.56
Mean systolic BP	0.12	0.13
Mean diastolic BP	0.11	0.15
Total cholesterol	0.22	0.17
LDL-cholesterol	0.11	0.42
HDL-cholesterol	0.20	0.27
Triglyceride	0.31	0.19
Creatinine	0.16	0.005
24-h urinary sodium excretion	0.21	0.0002

b

Variables	*Beta*	P-*value*
BMI	−0.14	0.050
Creatinine	0.17	0.003
24-h urinary sodium excretion	0.22	0.0001

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

daily salt intake and number of anti-hypertensive agents required for the treatment. Therefore, our findings may indirectly confirm the results of studies that propose high salt intake causes high BP, at least by pointing out the association between dietary salt intake and intensity of anti-hypertensive therapy. Interestingly, although patients with high salt intake attained BP levels similar to those in low- and medium-salt-intake groups, serum CRP levels and albuminuria were significantly increased in high-salt-intake group. Additionally, 24-h urinary sodium excretion was significantly correlated with serum CRP levels and albuminuria. These findings suggest that under similar BP conditions, high salt intake is associated with inflammation and renal injury reflected by increased albuminuria.

To our knowledge, this is the first study that specifically showed a relation between salt intake and CRP in a treated hypertensive population. A number of cross-sectional studies demonstrated higher levels of CRP in treated or untreated patients with primary hypertension compared with normotensive individuals.[17,26,27] However, greater plasma CRP concentrations among patients with hypertension might be explained by a clustering of common positive CRP covariates such as age, female sex, increased BMI and lipid concentrations.[28,29] In our study, we found urinary sodium excretion as an independent predictor of CRP, which suggests that high salt intake may be a novel covariate factor for high CRP levels in this population.

We also demonstrated that high salt intake was significantly associated with albuminuria independent of BP in treated hypertensive patients. This finding is consistent with the results of du Cailar *et al.*[7] that documented a significant association between urinary sodium excretion and albuminuria despite similar values of systolic arterial pressure in a group of normotensive subjects and patients with untreated hypertension. In a review of available published information, Jones-Burton *et al.*[30] also suggested that variations in dietary salt consumption directly influence albuminuria, with increasing salt intake associated with worsening albuminuria. Studies on animal models have proposed a link between dietary salt intake and target organ damage including ventricular hypertrophy and albuminuria. In these studies, high salt intake was found to be associated with increased collagen deposition and marked interstitial fibrosis in the left ventricle, glomeruli, renal tubules and in intramyocardial arteries and arterioles.[31] High dietary salt intake also produced arterial injury without increasing BP.[32] These effects of high salt intake on target organs are linked to the fibrogenic activity of transforming growth factor (TGF)-β1, as TGF-β1 production has been demonstrated to increase during high salt intake.[33,34] Indeed, the overexpression of TGF-β1 mRNA was demonstrated in the left ventricle and kidneys after a high-salt diet in animal studies.[31]

The present study demonstrated a positive correlation between albuminuria and serum CRP levels in treated hypertensive patients. CRP, a marker of systemic low-grade inflammation, and albuminuria are frequently elevated in essential hypertension and predict cardiovascular prognosis independent of conventional risk factors.[35] The relation between CRP and albuminuria in untreated hypertensive patients has been demonstrated in several reports.[35–38] The underlying pathophysiological mechanisms for the observed relation between albuminuria and inflammatory processes in the setting of essential hypertension have not been well defined. However, it has been proposed that low-grade inflammation seen in hypertensive subjects may increase the likelihood of increased glomerular leakage of albumin in response to BP.[35,39] This glomerular leakage may involve either increased transmission of systemic BP or decreased barrier function of the glomerulus due to inflammatory involvement.[38–40] In our study, regarding the near-normal BP levels of the patients under treatment in three salt-intake groups, serum CRP and urinary albumin levels were still higher in patients with high dietary salt intake. Furthermore, under the similar BP levels, urinary sodium excretion was correlated with both albuminuria and CRP. These findings suggest that increased glomerular leakage of albumin may reflect inflammation-mediated renal vascular injury rather than a response to elevated BP levels in our patient population. High dietary salt intake may contribute to this process directly via arterial injury or indirectly by augmenting the effects of inflammation.

However, the cross-sectional nature of our study limits the ability to conclude any causal relationship between salt intake, CRP levels and albuminuria. Moreover, CRP measurement was determined only once and we analyzed office BP measurements as ambulatory or home BP monitoring data of patients were not available. Given that these measurements may show intra-individual fluctuations, the accuracy of our results might be attenuated.

We did not find a correlation between albuminuria and age, gender, smoking, BMI, BP and lipid levels in this study. This may be related with hypertension treatment. Patients were prescribed many types of antihypertensive agents including ACE inhibitors, ARB, calcium channel blockers, beta-blockers and others. Effects of these drugs on albuminuria independent of BP-reducing effect may change the correlation analysis. In addition, sample size of the study and distribution characteristics of age, BMI, BP and lipid levels may also affect the results.

In conclusion, the major finding of the present study was that treated hypertensive patients with high dietary salt intake showed increased CRP concentrations and albuminuria. The relation of high salt intake with increased CRP and urinary albumin levels appeared independent of BP. These findings may suggest that under the similar BP conditions, high salt intake may be associated with enhanced inflammation and target organ damage reflected by increased albuminuria. Therefore, patients with high dietary salt intake may be at greater cardiovascular risk even though they are on appropriate anti-hypertensive medication. However, future, large and prospective studies are needed to confirm the

relation between salt intake, inflammation and cardiovascular diseases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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