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Sodium intake affects urinary albumin excretion especially in overweight subjects

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Summary. Verhave JC, Hillege HL, Burgerhof JGM, Janssen WMT, Gansevoort RT, Navis GJ, de Zeeuw D, de Jong PE for the PREVEND study group (Groningen University Institute of Drug Exploration (GUIDE), Groningen, The Netherlands). Sodium intake affects urinary albumin excretion especially in overweight subjects. *J Intern Med* 2004; **256**: 324–330.

Objectives. To examine the relationship between sodium intake and urinary albumin excretion, being an established risk marker for later cardiovascular morbidity and mortality.

Design. Cross-sectional cohort study using linear regression analysis.

Setting. University hospital outpatient clinic.

Subjects. A cohort drawn from the general population, consisting of 7850 subjects 28–75 years of age, all inhabitants of the city of Groningen, the Netherlands. The cohort is enriched for the presence of subjects with elevated urinary albumin concentration.

Results. The results show a positive relationship between dietary sodium intake and urinary albumin excretion. The association was independent of other cardiovascular risk factors (such as sex, age, blood pressure, body mass index (BMI), waist-to-hip ratio, serum cholesterol, plasma glucose and smoking) and other food constituents (calcium, potassium and protein). The relationship between sodium intake and urinary albumin excretion was steeper in subjects with a higher BMI compared with a lower BMI.

Conclusions. Sodium intake is positively related to urinary albumin excretion. This relation is more pronounced in subjects with a higher BMI. These results suggest that high sodium intake may unfavourably influences cardiovascular prognosis especially in overweight and obese subjects.

Keywords: cardiovascular risk factor, micro-albuminuria, obesity, urinary sodium excretion.

Introduction

The effect of sodium intake on cardiovascular morbidity and mortality has been a challenge to investigators since decades [1–3]. A high sodium intake can induce a rise in blood pressure (most likely in salt-sensitive subjects). This in turn is expected to result in an increase in cardiovascular

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morbidity and mortality. However, others do not agree with this line of reasoning and are not convinced of the benefit of reduction in sodium intake on population level [4]. Interestingly, evidence has emerged recently that the effect of high sodium intake on cardiovascular morbidity and mortality might not be mediated by changes in blood pressure. A large Finish prospective cohort study showed that high sodium intake predicted coronary heart disease and mortality, independent of blood pressure and other cardiovascular risk factors [5].

Albuminuria has been shown to be an early risk marker of later cardiovascular morbidity and mortality [6, 7]. Increased urinary albumin loss is thought to be the consequence of endothelial damage [8]. This endothelial damage may cause an increased susceptibility for cardiovascular and renal events in microalbuminuric subjects [7]. We tested whether an increased sodium intake is related to an increased urinary albumin excretion. As body mass index (BMI) is strongly associated with a higher urinary albumin excretion [9, 10], and as the relationship between sodium intake and cardiovascular morbidity and mortality has been observed particularly in obese subjects [11], we analysed the data specifically in relation to BMI. We thus hypothesized that a higher sodium intake is associated with a higher urinary albumin excretion, and that this association holds true especially in obese subjects. To study this, we used the data of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study.

Methods

Study design and population

As part of the PREVEND study, all inhabitants of the city of Groningen, the Netherlands, between 28 and 75 years of age, were asked to answer a short questionnaire and to send in a morning urine sample ($n = 85\,421$). The aim of the PREVEND study was to determine the relationship between albuminuria and cardiovascular and renal disease in the general population [12, 13]. Pregnancy and insulin treatment were exclusion criteria. Altogether, 40 856 subjects responded. All subjects with a urinary albumin concentration of ≥ 10 mg L^{-1} ($n = 7{,}768$) and a random sample of subjects with an albumin concentration <10 mg L^{-1} ($n = 3{,}395$) were invited to an outpatient clinic. The screening programme was completed by 8592 subjects. The subjects completed a questionnaire regarding demographics, cardiovascular and renal history, smoking status, and the use of oral hypoglycaemic, antihypertensive and lipid-lowering drugs. Anthropometrical measurements were performed, and blood pressure was measured during 10 min on 2 days with an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical INC., Tampa, FL, USA). Fasting blood samples were obtained and subjects submitted a 24-h urine collection, collected on two consecutive days. As we wanted to investigate the influence of sodium intake on albuminuria as a risk marker reflecting endothelial damage, we excluded for the present analyses 78 subjects because of a history of renal disease or proteinuria. Another 445 subjects were excluded because of leucocyturia and/or erythrocyturia, according to dipstick analysis (leucocytes >75 μL^{-1} or erythrocytes >50 μL^{-1}, or leukocytes $=75$ μL^{-1} and erythrocytes >5 μL^{-1}). These dipstick abnormalities indicate the possible presence of a urinary tract infection, which makes albumin measurements unreliable. The present analyses contained 7850 subjects because 219 subjects had missing information on one of the variables included in the regression model. All subjects gave written informed consent. The local medical ethics committee approved the PREVEND study and the performance of the project was in accordance with the guidelines of the Declaration of Helsinki.

Measurements and definitions

Creatinine assessments in blood and urine, serum cholesterol and glucose were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automated enzymatic method. The intra- and inter-assay variation coefficient of serum creatinine was 0.9 and 1.1%, respectively. For urinary creatinine the coefficients were 0.9 and 2.9%. Renal function is measured as creatinine clearance, which is given as the mean of two 24 h urinary creatinine excretions divided by plasma creatinine. Urinary leucocyte and erythrocyte measurements were carried out by Nephur-test + leuco sticks (Boehringer Mannheim, Mannheim, Germany). Urinary albumin concentration

was determined by nephelometry with a threshold of 2.3 mg L^{-1} and intra-assay and inter-assay coefficients of variation of less than 2.2 and 2.6% (Dade Behring Diagnostic, Marburg, Germany). Sodium, calcium, potassium and urea were determined in urine with an MEGA clinical chemistry analyser (Merck, Darmstadt, Germany). Sodium and potassium were determined by indirect potentiometry, calcium by a photometric test with an o-Cresolphthalein complex and urea by a photometric test with the uease-GIDH method. Urinary albumin, sodium, calcium, potassium and urea are given as the mean of the two 24 h urine excretions. Body mass index was calculated as weight (kg) divided by square of height (m^2). Waist-to-hip ratio was calculated as the ratio of minimal waist circumference and maximal hip circumference. Blood pressure values given are the mean of the last two recordings of both days. Smoking was defined as current smoking or cessation of smoking less than a year before the study.

Statistical analyses

Our null hypothesis was that there is no relationship between the variables of interest and urinary sodium excretion (general linear model). A chi-square test was applied to investigate whether the number of men and smokers had a linear trend over the quintiles of urinary sodium excretion.

For the screening of the PREVEND study we selected subjects with an elevated urinary albumin excretion in order to acquire sufficient subjects with microalbuminuria. We used design-based linear regression [14] using weighing factors to correct for the oversampling of subjects with an elevated urinary albumin excretion. Analyses were conducted using 'svy' commands for analysing complex survey design data (STATA, Texas version 7.0). The dependent variable in the model was urinary albumin excretion. The independent variables in the model were urinary sodium excretion, sex, age, systolic and diastolic blood pressure, BMI, waist-to-hip ratio, plasma glucose, serum cholesterol, smoking, creatinine clearance, the use of antihypertensive, lipid lowering or hypoglycaemic medication, and urinary potassium, calcium and urea excretion. Visual inspection of the data revealed a curved relationship between urinary albumin excretion and some of the explanatory variables. Examination of the curvature was performed by graphical interpretation and by including a quadratic term of the variable and by testing its inclusion in the model using the linear regression model. Interaction (effect modification) between the various explanatory variables was tested by entering product-terms into the regression equation. A two-sided $P < 0.05$ was considered significant. The comparison between two models with more than one degree of freedom was carried out by an adjusted Wald test [15].

Results

Population characteristics

Table 1 shows the characteristics of the study population, when divided into quintiles according to urinary sodium excretion. Men had higher sodium excretion in comparison with women. Urinary albumin excretion increased over the quintiles of urinary sodium excretion. The increase in systolic and diastolic blood pressure over the urinary sodium quintiles is not present after tabulation of men and women separately. Older subjects consumed less sodium than younger subjects and subjects who consumed more sodium were more likely to be obese and to have a higher waist-to-hip ratio. Cholesterol, creatinine clearance, calcium, potassium and urea excretion showed a positive relationship with urinary sodium, whereas the relationship between smoking and sodium excretion was negative.

Urinary albumin excretion and sodium intake

To test the relationship between urinary albumin excretion and sodium intake, we performed a linear regression analyses. Because urinary albumin excretion has a skewed distribution we used a double natural logarithm for an optimal residual analysis. For the same reason, plasma glucose was transformed by a natural logarithm. All effects were transposed back from the logarithmic scale and are reported in absolute terms of change in urinary albumin excretion per unit increase of each explanatory variable. In the univariate model urinary sodium excretion was positively associated with urinary albumin excretion (r^2 0.05; $P < 0.05$) (Fig. 1). In the multivariate model urinary sodium remained positively associated with urinary albumin

Table 1 Population characteristics according urinary sodium excretion (mmol 24 h^{-1}) in quintiles

	Urinary sodium in quintiles					*P*-value for trend
	1	2	3	4	5	
Mean (max–min)						
Urinary sodium excretion (mmol 24 h^{-1})	79.5 (<99.4)	112.5 (99.4–124.8)	136.9 (124.8–149.4)	163.9 (149.5–180.6)	220.1 (>180.7)	
Men (*n*)	475	686	807	982	1215	<0.001
Women (*n*)	1138	926	807	631	398	
Median (IQR)						
Urinary albumin excretion (mg 24 h^{-1})	7.5 (5.3–13.3)	8.5 (6.0–15.0)	9.4 (6.3–17.2)	9.8 (6.5–18.2)	11.1 (7.3–21.7)	<0.001
Mean (SD)						
Systolic blood pressure (mmHg)	128 (22)	127 (20)	129 (21)	130 (19)	132 (18)	<0.001
Diastolic blood pressure (mmHg)	73 (10)	73 (10)	74 (10)	74 (10)	76 (9)	<0.001
Age (years)	50 (13)	49 (13)	49 (13)	49 (12)	48 (12)	<0.001
Body mass index (kg m^{-2})	24.9 (3.9)	25.3 (3.9)	25.9 (4.1)	26.4 (4.0)	27.8 (4.7)	<0.001
Waist-to-hip ratio	0.85 (0.09)	0.86 (0.09)	0.88 (0.09)	0.89 (0.09)	0.92 (0.09)	<0.001
Cholesterol (mmol L^{-1})	5.6 (1.2)	5.6 (1.1)	5.6 (1.1)	5.7 (1.1)	5.7 (1.1)	0.03
Glucose (mmol L^{-1})	4.8 (0.9)	4.8 (1.0)	4.9 (1.2)	4.9 (1.2)	5.1 (1.5)	<0.001
Creatinine clearance (mL min^{-1})	85.3 (22.0)	95.2 (21.3)	102.0 (21.7)	109.9 (22.8)	124.7 (27.5)	<0.001
Urinary calcium excretion (mmol 24 h^{-1})	2.9 (1.5)	3.5 (1.6)	3.9 (1.8)	4.5 (2.0)	5.2 (2.4)	<0.001
Urinary potassium excretion (mmol 24 h^{-1})	58.1 (19.0)	66.6 (17.9)	71.4 (18.3)	77.1 (20.0)	84.7 (21.1)	<0.001
Urinary urea excretion (mmol 24 h^{-1})	267.5 (78.2)	318.8 (78.3)	351.5 (77.7)	389.5 (83.6)	454.9 (102.5)	<0.001
Smoking (%)	42.7	37.3	36.4	36.2	36.8	0.001

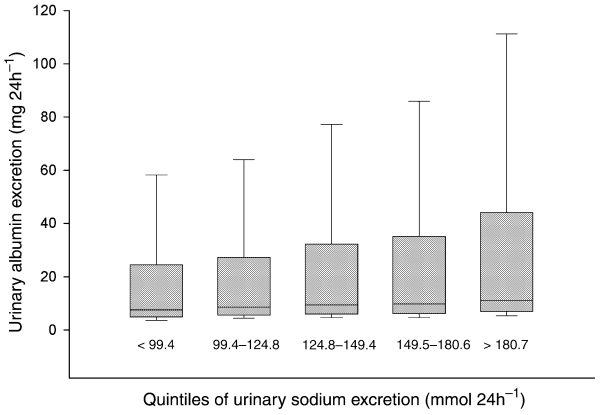

Fig. 1 Box-and-whisker plots of urinary albumin excretion for the quintiles of urinary sodium excretion. The values beneath the plots represent the range of urinary sodium excretion in the corresponding quintile.

excretion after correction for confounders (sex, age, systolic and diastolic blood pressure, BMI, waist-to-hip ratio, creatinine clearance, plasma glucose, smoking, urinary calcium, potassium, urea excretion and the use of antihypertensive, lipid lowering and hypoglycaemic medication) (r^2 0.22; $P < 0.05$). Serum cholesterol, antihypertensive, lipid lowering and hypoglycaemic medication did not significantly contribute to the multivariate model.

Interaction of sodium and body mass index on urinary albumin excretion

The interaction of urinary sodium and BMI was statistically significant ($P < 0.05$) and the r^2 of the multivariate model augmented to 0.24 when this interaction term was added. For a higher sodium intake, subjects with an elevated BMI had a higher urinary albumin excretion than subjects with a lower BMI. The aforementioned cardiovascular risk factors were all positively related to urinary albumin excretion in the multivariate model. Other indicators of food constituents (urinary calcium, potassium and urea) also had a positive association with urinary albumin excretion. The effect of sodium intake on urinary albumin excretion was however independent of these other food constituents (Fig. 2). After correction of the regression model for the presence of diabetes the interaction of sodium intake and BMI on albuminuria remains present, indicating that the results are not due to an interaction limited to diabetic persons in our population.

Discussion

This study shows that an elevated urinary sodium excretion, which reflects a higher sodium intake, is

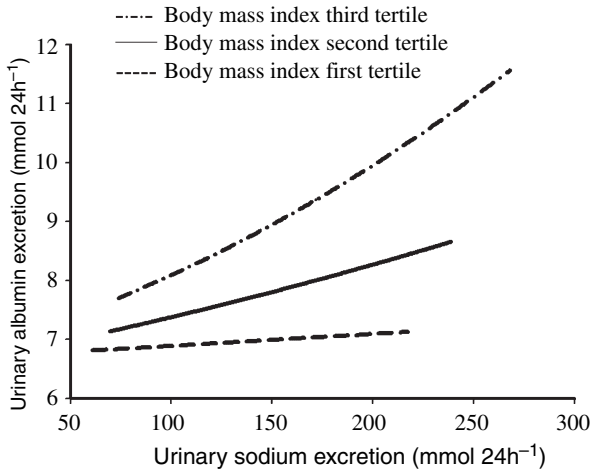

Fig. 2 The interaction of body mass index (BMI) and urinary sodium excretion on urinary albumin excretion adjusted for cardiovascular risk factors and other food constituents, a graphical interpretation of the regression equation. For every separate tertile of BMI (first tertile 16.3–24.0 kg m^{-2}, second tertile 24.0–27.3 kg m^{-2}, third tertile 27.3–63.6 kg m^{-2}) the mean of the covariates are included in the regression formula.

independently associated with an increase in urinary albumin excretion. This relation is modified by BMI. For the same sodium intake, obese and even mildly overweight subjects have a higher urinary albumin excretion than lean subjects. This phenomenon is more pronounced at a high sodium intake. As an elevated urinary albumin excretion is thought to reflect endothelial damage and to predict cardiovascular morbidity and mortality [16], our data suggest that high sodium intake is independently related to an unfavourable cardiovascular prognosis, especially in overweight and obese subjects. The relationship between sodium and urinary albumin excretion was independent of other food constituents.

A similar positive association between sodium intake and urinary albumin excretion was recently described by du Cailar *et al.* [17]. These authors found an interaction between sodium intake and systolic blood pressure on urinary albumin excretion. At variance with our data, they found that sodium intake amplified the effect of blood pressure on urinary albumin excretion. This discrepancy may be caused by differences between populations under study. The population of du Cailar was from an outpatient clinic to which patients were referred for detection of cardiovascular risk factors. Consequently, the prevalence of hypertension in their population was higher with 60% being hypertensive (defined as a systolic blood pressure >140 mmHg, a diastolic blood pressure >90 mmHg without antihypertensives), when compared with 30% in our population using the same definitions.

The association between sodium excretion and urinary albumin excretion was independent of the other food constituents tested. We therefore argue that it is the intake of sodium, and not of protein (estimated from urea excretion), calcium or potassium that induces this detrimental effect. Our findings of an unfavourable effect of sodium intake on urinary albumin excretion in overweight and obese subjects agree with the results of the NHANES I study. In that study a positive and independent relationship was shown between dietary sodium intake and cardiovascular disease risk (independent of baseline systolic blood pressure) in overweight adults. No relationship was found between sodium intake and risk for cardiovascular disease in non-overweight persons [11]. A limitation of that study is, however, that sodium intake was estimated by dietary recall, which is less reliable as a measure for actual sodium intake than 24 h urine collections [18].

What could be the mechanisms underlying the association of sodium intake with urinary albumin excretion especially in obese subjects? The mechanism behind leakage of urinary albumin is not clear and renal haemodynamic factors could be important. Obese subjects have a higher glomerular filtration rate and filtration fraction than lean subjects [19]. This pattern, reflecting altered afferent/efferent balance, is already present in the overweight range [20]. This implies a constriction of the efferent or dilatation of the afferent arterioles, resulting in hyperfiltration. Recent studies suggested that endocrine effects of adipose tissue, leading to neurohormonal system activation, may be involved in the altered water and sodium homeostasis, and regulation of intraglomerular pressure in overweight and obesity [21, 22]. The observation that the relationship between sodium excretion and albuminuria was independent of blood pressure suggests that the detrimental effect of sodium is not solely pressure-mediated. The positive association between urinary sodium excretion and urinary albumin excretion could be explained by a detrimental effect of sodium to the arterial vessel wall [23]. As a consequence of generalized endothelial

dysfunction, albumin may leak through the blood vessel wall, detectable in the urine by the presence of albumin [16].

It is important to note that our study has limitations. Both sodium intake, measured as urinary sodium excretion, and urinary albumin excretion were measured from the same 24 h urine sample. The observed relationship between sodium excretion and albuminuria might thus be due to an artefact in 24 h urine collection. We conducted a set of sensitivity analyses to evaluate the robustness of our conclusions. We repeated the analyses and excluded subjects in whom both 24 h creatinine excretions differed by more than 20, 10 or 5%, respectively. The obtained results were essentially the same as in the original analyses.

Another limitation is the cross-sectional design of our study. We cannot draw conclusions on a possible cause-and-effect relationship. Moreover, our study cannot determine whether lowering sodium intake will lower urinary albumin excretion and eventually reduce the risk of cardiovascular diseases. Long-term dietary intervention studies that are adequately powered to study this issue will however be difficult to perform.

What may be the clinical consequences of our findings? First, they suggest that if a patient is known to have an elevated urinary albumin excretion, dietary sodium restriction may be advisable to lower the risk for cardiovascular events. Secondly, this seems especially true in case of overweight or obese subjects. Finally, studies have been performed that show a beneficial effect of dietary caloric restriction on cardiovascular risk [24]. Studies on weight loss should also consider whether the beneficial effect is due to the lowering of body weight, or to the fact that such diets also result in a lower sodium intake. Obesity activates the renin–angiotensin system which might increase tubular reabsorption of sodium [25]. As the efficacy of angiotensin-converting enzyme (ACE) inhibitors may be enhanced on low sodium diet [26], obese subjects requiring ACE inhibitors to lower proteinuria should be instituted either on a low-sodium diet and/or on diuretics [27].

In conclusion, we found in this cross-sectional population-based study that sodium intake is positively associated with urinary albumin excretion, being a risk marker for cardiovascular morbidity and mortality. The relationship between sodium intake and urinary albumin excretion was steeper in overweight and obese subjects in comparison with lean subjects. This association was furthermore blood pressure independent. We therefore hypothesize that sodium intake may have a direct harmful effect on the cardiovascular system, especially in overweight subjects.

Conflict of interest

No conflict of interest was declared.

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