Diabetologia (2004) 47:300–303
DOI 10.1007/s00125-003-1303-5

Diabetologia

Short Communication

Effect of sodium intake on blood pressure and albuminuria in Type 2 diabetic patients: the role of insulin resistance

M. Vedovato[1] · **G. Lepore**[2] · **A. Coracina**[1] · **A. R. Dodesini**[2] · **E. Jori**[1] · **A. Tiengo**[1] · **S. Del Prato**[3] · **R. Trevisan**[2]

[1] Unit for Metabolic Disease, Department of Clinical and Experimental Medicine, University of Padua, Padua, Italy
[2] U.O. Diabetologia, Ospedali Riuniti di Bergamo, Bergamo, Italy
[3] Department of Endocrinology and Metabolism, Section of Diabetes, University of Pisa, Pisa, Italy

Abstract

Aims/hypothesis. This study was done to measure the effect of Na^+ intake on blood pressure and albuminuria, in relation with insulin sensitivity and kidney haemodynamics, in Type 2 diabetic patients with and without microalbuminuria.
Methods. Type 2 diabetic patients, 20 with microalbuminuria, 21 without, spent two consecutive 7-day periods, one on a high (250 mmol), the other on a low-Na^+ (20 mmol) diet. Body weight, 24-h blood pressure and albuminuria were measured at the end of each period. At the end of high-Na^+ diet insulin sensitivity (euglycaemic insulin clamp; 2 $mU \cdot kg^{-1} \cdot min^{-1}$) and kidney haemodynamics were measured in nine patients from each group.
Results. Switching from low to high-Na^+ diet resulted in an increase in blood pressure (7.4±4.7 mmHg; $p<0.001$), body weight (1.9±0.4 kg; $p<0.05$) and albuminuria [from 80 (31–183) μg/min to 101 (27–965) μg/min; $p<0.01$) in patients with microalbuminuria. No changes occurred in patients without microalbuminuria. Patients with microalbuminuria also had greater intraglomerular pressure (44±1 mmHg vs 36±1; $p<0.001$), calculated from glomerular filtration rate, renal plasma flow, plasma protein concentration and the relationship between pressure and natriuresis. In these patients insulin sensitivity was lower (5.16±49 vs 7.36±0.63 $mg \cdot kg^{-1} \cdot min^{-1}$; $p=0.007$). Urinary albumin excretion ($r=0.40$; $p=0.009$) and insulin sensitivity ($r=-0.59$; $p=0.01$) were correlated with intraglomerular pressure.
Conclusion/interpretation. High salt intake increases blood pressure and albuminuria in Type 2 diabetic patients with microalbuminuria. These responses are associated with insulin resistance and increased glomerular pressure. Insulin resistance could contribute to greater salt sensitivity, increased glomerular pressure and albuminuria. [Diabetologia (2004) 47:300–303]

Keywords Microalbuminuria · Salt sensitivity · Type 2 diabetes · Glomerular filtration rate · Renal plasma flow · Intraglomerular pressure · Insulin resistance

Microalbuminuria in Type 2 diabetic patients, a powerful predictor of renal disease and cardiovascular morbidity and mortality, is associated with hypertension [1]. Although hypertension is associated with an increased exchangeable sodium pool in diabetic patients [2], few studies have addressed the role of sodium intake on blood pressure and kidney haemodynamics in Type 2 diabetes. Recently it was shown that in Type 1 and in Type 2 diabetic patients with increased albumin excretion the sensitivity of blood pressure to salt intake is greater than in patients with normoalbuminuria [3, 4].

The association between reduced insulin resistance and salt sensitivity has prompted the hypothesis that hyperinsulinaemia could be involved in the sensitivity of blood pressure to salt intake [4].

The purpose of the present study was to measure the effect of salt intake on blood pressure and albumin excretion rate (AER) in Type 2 diabetic patients with

Received: 2 June 2003 / Revised: 27 October 2003
Published online: 24 December 2003

R. Trevisan (✉)
U.O. Diabetologia, Ospedali Riuniti di Bergamo,
Largo Barozzi 1, 24128 Bergamo, Italy
E-mail: rtrevisan@ospedaliriuniti.bergamo.it

Abbreviations: GFR, Glomerular filtration rate · PGC, intraglomerular pressure · AER, albumin excretion rate

and without microalbuminuria, and to determine any possible relationship with insulin sensitivity.

Subjects and methods

Recruitment of subjects. We recruited 20 Type 2 diabetic patients with persistent microalbuminuria and blood pressure below 140/90 mmHg in the absence of antihypertensive treatment from the Diabetes Clinics at the Padova University Hospital and at the Bergamo Hospital. For comparison we recruited 21 Type 2 diabetic patients, who were matched for age, sex distribution, BMI, duration of diabetes and blood pressure but had normal albumin excretion (Table 1). All patients gave written informed consent before participating in the study, which was approved by the local ethics committees and complied with the Declaration of Helsinki as revised in 2000.

Study protocol. All subjects underwent, in random order, two consecutive 7-day diet periods with low or high sodium content respectively. The low-sodium diet contained 25 mmol sodium chloride, 60 mmol potassium and 20 mmol calcium. The high-sodium diet was exactly the same, the only exception being that the daily amount of sodium chloride was 250 mmol (given as 500 mg sodium chloride tablets). Compliance with diet was assessed by 24-h urinary sodium excretion during the last 3 days of each diet period. Arterial blood pressure was measured by 24-h ambulatory blood pressure measurements using a Takeda TM2420 device (A&D Medical, Tokyo, Japan) at the end of each diet period.

In nine patients with and nine without microalbuminuria, insulin sensitivity and kidney function were measured at the end of the high-salt diet. On the evening of day 6 of the high-salt diet period, their usual antidiabetic treatment was stopped and an intravenous variable insulin infusion (starting rate of 1 U/h) was begun to achieve and maintain overnight plasma glucose concentrations between 5 and 7 mmol/l. At 8 a.m. whole body insulin sensitivity was measured using the euglycaemic (≈5 mmo/l) hyperinsulinaemic (≈200 mU/L) clamp technique [4]. Glomerular filtration rate (GFR) and effective renal plasma flow were measured by plasma clearances of ^{51}Cr-EDTA and of para-aminohippurate [4].

Table 1. Clinical features of Type 2 diabetic patients with and without microalbuminuria

	Type 2 diabetic patients with micro-albuminuria	Type 2 diabetic patients without micro-albuminuria
Men/women	15/5	16/5
Age (years)	57±1	60±2
Duration of diabetes (years)	9±2	10±3
Body mass index (kg/m^2)	29±2	28±2
HbA_{1c} (%)	8.2±0.6	8.3±0.8
Systolic BP (mmHg)	130±2	126±2
Diastolic BP (mmHg)	80±2	79±2
Albumin excretion rate (μg/min)	91 (43–180)	10 (3–18)

Data are means ± SEM, except for albumin excretion rate, which is given as median and range

Analytical methods. Plasma free insulin, renin activity, aldosterone and urinary albumin concentrations were measured by standard radioimmunoassay procedures [4]. Plasma and urine sodium and potassium concentrations were measured by flame photometry. Glycated haemoglobin was measured by HPLC assay (normal range 4–6.5%).

Curves expressing the relationship between pressure and natriuresis were produced for each patient studied by plotting sodium excretion rate as a function of mean blood pressure, measured at the end of each diet period. The intraglomerular pressure (PGC) was estimated indirectly from the relationship between pressure and natriuresis, as described [5].

Statistical analysis. All calculations were done using the SPSS/WIN program version 6.0 (SPSS, Chicago, Ill., USA). Mean blood pressure was calculated as diastolic values plus one third of the difference between systolic and diastolic blood pressure. All data are expressed as means ± SEM. For AER the values are expressed as median with the 25th and the 75th percentiles, unless otherwise stated. Differences between means of parameters within groups were tested for significance using the paired *t* test or analysis of variance; between-group differences were assessed using the unpaired *t* test. Linear regression analysis was done to determine the correlation between different parameters. Differences were taken to be significant with a *p* value of less than 0.05.

Results

Blood pressure, kidney haemodynamics, insulin sensitivity. At the end of each diet period there was no difference between the two groups in mean 24-h urinary sodium excretion. Potassium excretion remained constant in both groups. Plasma concentrations of aldosterone and renin activity were similar in normo- and microalbuminuric patients.

Type 2 diabetic patients with microalbuminuria gained more weight when they achieved high sodium balance than patients without microalbuminuria (2.2±0.26 vs 0.5±0.16 kg; $p<0.0001$).

No differences in blood pressure were observed between microalbuminuric and normoalbuminuric patients after a low-sodium diet (Fig. 1a). In contrast, blood pressure values were higher in microalbuminuric patients after the high-sodium diet period. On switching from the low to high-sodium diet, 24-h mean arterial blood pressure increased from 95±2 mmHg to 103±2 ($p<0.0001$) in patients with microalbuminuria, a percentage increase of 7.1±0.9%. In contrast, no significant change occurred in patients with normoalbuminuria (from 94±1 to 95±1 mmHg; 1.3±0.8%). The slope of the pressure-natriuresis curve was less steep for patients with microalbuminuria (Fig. 1b). The calculated PGC was higher in patients with microalbuminuria (44.08±1.39 mmHg) than in those without (36.16±0.90 mmHg; $p<0.001$).

The albumin excretion rate did not change in normoalbuminuric patients after the high-salt diet period [from 8 (5–12) μg/min after the low-sodium diet period to 9 (6–12) μg/min after the high-sodium diet period]. A significant increase in urinary AER occurred in

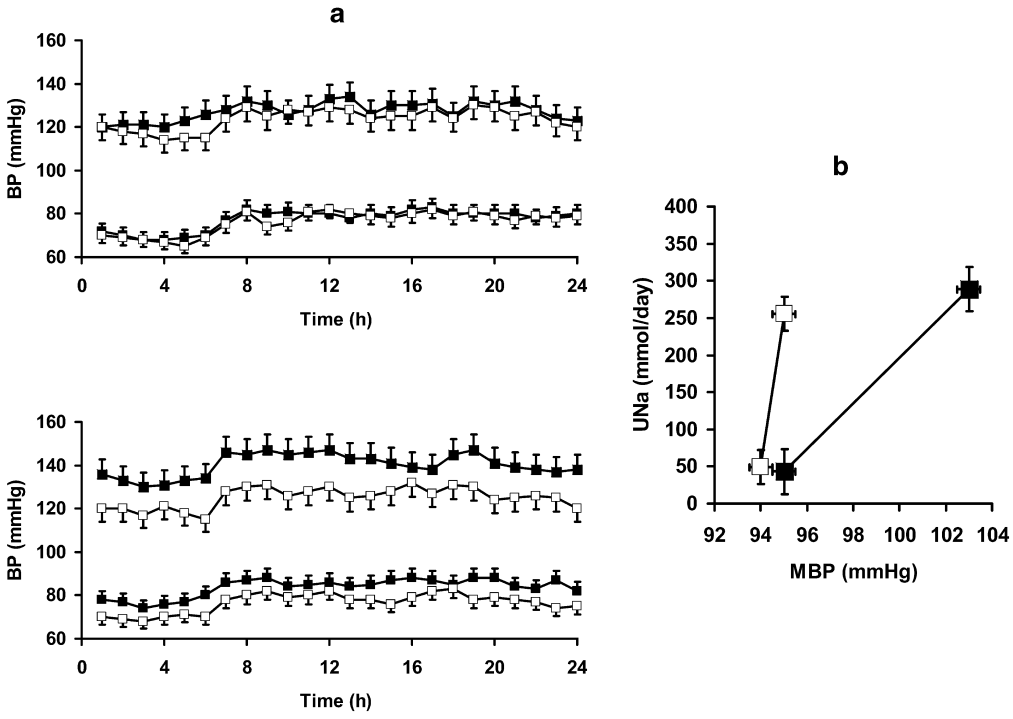

Fig. 1. a 24-h profile of mean ± SEM of mean systolic and diastolic blood pressure in Type 2 diabetic patients with (■) and without (□) microalbuminuria after a low (upper panel) or a high-sodium diet (lower panel). **b** Association (pressure-natriuresis curve) between sodium urinary excretion (UNa) and mean blood pressure (MBP) in Type 2 diabetic patients with (■) and without (□) microalbuminuria

microalbuminuric patients [from 80 (37–114) μg/min to 108 (84–178) μg/min; $p<0.001$].

After the high-salt diet, GFR values were comparable in the two groups (132±9 ml·min^{-1}·1.73 m^{-2} in Type 2 diabetic patients with microalbuminuria vs 127±11 in those without microalbuminuria). Renal plasma flow was lower in the microalbuminuric group (574±30 ml·min^{-1}·1.73 m^{-2}) than in normoalbuminuric patients (788±60; $p<0.05$). As a result, the filtration fraction was greater in microalbuminuric patients (0.23±0.01) than in normoalbuminuric patients (0.16±0.01; $p<0.01$).

During the euglycaemic hyperinsulinaemic clamp, whole-body glucose disposal was lower in the microalbuminuric (5.16±0.49 mg·kg^{-1}·min) than in normoalbuminuric patients (7.36±0.63) ($p= 0.007$).

Correlations. When data were pooled, salt-induced changes in 24-h mean blood pressure were directly related to the increase in AER observed after a high-sodium diet (r=0.41; p=0.008). The PGC calculated at the end of the high-salt diet was directly associated with AER (r=0.40; p=0.009). In patients in whom insulin sensitivity was measured the PGC (r=–0.59; p=0.01) and salt-induced changes in mean blood pressure (r=–0.51; p=0.01) were inversely related to insulin sensitivity.

Discussion

This study shows that after a high-sodium diet microalbuminuric Type 2 diabetic patients have a blood pressure which is sensitive to salt intake and an increased AER. These features are strongly associated with greater insulin resistance.

It is unlikely that these results are accounted for by impaired renal function or differences in the renin-angiotensin system, as GFR was normal in all patients and plasma concentrations of aldosterone and active renin did not differ between patients with and without microalbuminuria.

We also found that sodium sensitivity in microalbuminuric patients was associated with increased glomerular pressure and with increased albuminuria after the high-sodium diet. The observation that renal plasma flow was lower in microalbuminuric Type 2 diabetic patients is consistent with the blunted vasodilator renal plasma flow response to a high-sodium diet observed in another study [6]. This is of clinical relevance, as the increase in filtration fraction and in albuminuria after high-sodium diet suggests that dietary sodium has a detrimental effect on the kidney susceptible to development of diabetic nephropathy. Although PGC was only calculated, our results, which are similar to those found in Japanese Type 2 diabetic patients [5], reinforce the evidence that systemic hypertension is transmitted to the single glomerulus in such a way as to lead to hyperperfusion and increased capillary pressure.

It is possible that salt sensitivity and insulin resistance interact to increase glomerular permeability and PGC, both of which favour albumin leakage [7]. The association between salt sensitivity and insulin resis-

tance has been explained as an effect of compensatory hyperinsulinaemia in sustaining renal tubular reabsorption of sodium [8]. As suggested by a greater gain in body weight, sodium retention occurs in Type 2 diabetic patients with microalbuminuria after the high-sodium diet. In Type 2 patients, endothelial-dependent vascular relaxation is impaired and associated with insulin resistance. The resistance of vascular smooth muscle cells to insulin vasodilator effect could therefore account for the rise in blood pressure after a sodium load as a consequence of sodium retention and increased peripheral resistance.

We suggest that the sensitivity of blood pressure to salt is an intermediate phenotype which could prove useful in identifying Type 2 diabetic patients at increased risk for cardiorenal complications. Our results provide further support for encouraging Type 2 diabetic patients with microalbuminuria to reduce salt intake, because such a reduction could help preserve renal function, especially when associated with ACE-inhibition treatment, as recently shown [9]. Our data provide insights into the potential mechanisms of the beneficial effects of low-dose diuretic therapy, alone or in combination with ACE-inhibitors in the treatment of hypertension and microalbuminuria in diabetes [10].

Acknowledgements. This study was supported by a research grant from the University of Padua, Italy.

References

1. Mogensen CE (1999) Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas. Diabetologia 42:263–285
2. Beretta-Piccoli C, Weidmann P (1982) Body sodium-volume state in nonazotemic diabetes mellitus. Miner Electrolyte Metab 7:36–47
3. Imanishi M, Yoshioka K, Okumura M et al. (2001) Sodium sensitivity related to albuminuria appearing before hypertension in Type 2 diabetic patients. Diabetes Care 24:111–116
4. Trevisan R, Bruttomesso D, Vedovato M et al. (1998) Enhanced responsiveness of blood pressure to sodium intake and to angiotensin II is associated with insulin resistance in IDDM patients with microalbuminuria. Diabetes 47: 1347–1353
5. Imanishi M, Yoshioka K, Konishi Y et al. (1999) Glomerular hypertension as one cause of albuminuria in type II diabetic patients. Diabetologia 42:999–1005
6. De'Oliveira JM, Price DA, Fisher ND et al. (1997) Autonomy of the renin system in Type II diabetes mellitus: dietary sodium and renal hemodynamic responses to ACE inhibition. Kidney Int 52:771–777
7. Bianchi S, Bigazzi R, Quinones Galvan A et al. (1995) Insulin resistance in microalbuminuric hypertension. Sites and mechanisms. Hypertension 26:789–795
8. Trevisan R, Fioretto P, Semplicini A et al. (1990) Role of insulin and atrial natriuretic peptide in sodium retention in insulin-treated IDDM patients during isotonic volume expansion. Diabetes 39:289–298
9. Houlihan CA, Allen TJ, Baxter AL et al. (2002) A low-sodium diet potentiates the effects of losartan in type 2 diabetes. Diabetes Care 25:663–671
10. Mogensen CE, Viberti G, Halimi S et al. (2003) Effect of low-dose perindopril/indapamide on albuminuria in diabetes. Preterax in Albuminuria Regression (PREMIER) Study Group. Hypertension 41:1063–1071