

Altered renal sodium handling in men with abdominal adiposity: a link to hypertension

Pasquale Strazzullo^a, Gianvincenzo Barba^b, Francesco P. Cappuccio^c, Alfonso Siani^b, Maurizio Trevisan^d, Eduardo Farinero^e, Ermenegilda Pagano^a, Antonio Barbato^a, Roberto Iacone^a and Ferruccio Galletti^a

Objectives Central adiposity, insulin resistance and hypertension are clearly interrelated but the mechanisms underlying this association have not been thoroughly elucidated. As renal sodium handling plays a central role in salt-sensitive forms of hypertension, we investigated the relation of renal tubular sodium handling to abdominal adiposity, blood pressure and insulin sensitivity.

Design Population-based study.

Participants Five hundred and fifty-five untreated Olivetti male workers, aged 25–75 years.

Setting Olivetti factory medical centers in Pozzuoli and Marcianise (Naples, Italy)

Main outcome measures Anthropometric indices, serum insulin, homeostatic model assessment index of insulin sensitivity, blood pressure, fractional excretions of uric acid and exogenous lithium (as markers of renal tubular sodium handling).

Results In univariate analysis, measures of central adiposity (i.e. sagittal abdominal diameter and umbilical circumference) were directly correlated with serum insulin ($P < 0.001$) and blood pressure levels ($P < 0.001$) and inversely associated with the fractional excretions of uric acid and lithium ($P = 0.01–0.001$). In multiple linear regression analysis, the same anthropometric indices but not the measures of peripheral adiposity (arm circumference and tricipital skinfold thickness), were significant predictors of the fractional excretion of uric acid

and lithium, independently of age, blood pressure and serum insulin levels ($P = 0.01–0.001$).

Conclusions Abdominal adiposity was associated with altered renal tubular sodium handling apart from insulin resistance and high blood pressure. The data indicate that men with prevalent abdominal adiposity have an enhanced rate of tubular sodium reabsorption, mainly at proximal sites. These findings provide a possible mechanistic link between central adiposity and salt-dependent hypertension. *J Hypertens* 19:2157–2164 © 2001 Lippincott Williams & Wilkins.

Journal of Hypertension 2001, 19:2157–2164

Keywords: blood pressure, abdominal adiposity, insulin resistance, renal sodium handling, salt-sensitive hypertension

^aDepartment of Clinical and Experimental Medicine, Unit of Clinical Genetics and Pharmacology, Hypertension and Mineral Metabolism, 'Federico II' University of Naples Medical School, Naples, Italy, ^bInstitute of Food Science and Technology, CNR, Avellino, Italy, ^cDepartment of General Practice and Primary Care, St Georges' Hospital Medical School, University of London, London, UK, ^dDepartment of Social and Preventive Medicine, State University of New York at Buffalo, Buffalo, New York, USA and ^eDepartment of Preventive Medical Sciences, 'Federico II' University of Naples Medical School, Naples, Italy.

Sponsorship: The study was supported in part by grants from MURST (Italian Ministry of University and Scientific and Technological Research COFIN 1998) and Modinform s.p.a. (Olivetti group).

Correspondence and requests for reprints to P. Strazzullo, Department of Clinical and Experimental Medicine, Unit of Clinical Genetics and Pharmacology, Hypertension and Mineral Metabolism, 'Federico II' University of Naples, via S. Pansini 5, 80131 Naples, Italy.
Tel: +39 081 746 3686; fax: +39 081 546 6152; e-mail: strazzul@unina.it

Received 17 April 2001 **Revised** 18 July 2001
Accepted 18 July 2001

Introduction

Central adiposity predicts high blood pressure in clinical and epidemiological studies [1–3]. Insulin resistance and hyperinsulinemia are frequent companions in this association [1,4–7] and, in turn, are found with increased frequency in patients with essential hypertension [8–11]. The mechanisms of these multiple relationships are not thoroughly clarified. Experimentally induced obesity in the dog is associated with development of hypertension together with insulin resistance, sympathetic activation and evidence of

chronic sodium retention [12–14]. A trend to sodium and water retention has been called upon also as a plausible mechanistic link between obesity, insulin resistance/hyperinsulinemia and high blood pressure in man [15–23]; however, this remains a controversial issue [24] since no evidence has been provided of chronically altered renal sodium handling in relation to central adiposity. We have previously shown that a group of overweight men selected for having high levels of plasma trygliceride and uric acid and low levels of plasma high density lipoprotein-cholesterol (a

cluster of abnormalities suggestive of insulin resistance) had reduced fractional excretion of uric acid and of exogenous lithium compared to a group of age-matched control subjects [25]; this finding suggests that they had an increased rate of renal tubular sodium reabsorption, more probably at proximal sites. In that study, however, body fat distribution and serum insulin levels were not measured to further substantiate this hypothesis.

More recently, we examined these associations through the study of a large sample of participants undergoing follow-up examination in the framework of the Olivetti Heart Study. The purpose of the analysis presented here was to determine whether an alteration of the renal tubular handling of sodium is associated with central adiposity and/or insulin resistance.

Methods

Population

The study was performed at the Olivetti factories of Pozzuoli (Naples) and Marcianise (Caserta) and was part of a prospective investigation on the prevalence of cardiovascular risk factors in southern Italy initiated in 1975, involving the participation of the Olivetti factory male workforce. The methodology of the study has been described in detail elsewhere [26]. The data presented here were collected during the 1994–95 follow-up examination. Between May 1994 and December 1995, a cohort of 1079 men, aged 25–75 years (mean \pm SD = 51.8 ± 7.5) were examined. They represented over 95% of the male workforce employed at the time. For the purpose of the present report, we excluded 230 participants who were receiving pharmacological treatment for hypertension ($n = 195$) or for type 1 or 2 diabetes mellitus ($n = 35$), 33 whose fasting blood glucose concentration was above the diagnostic limit for diabetes mellitus (fasting serum glucose > 7.7 mmol/l or 126 mg/dl), 186 who refused to take the lithium tablet or did not provide a urine sample and 75 subjects whose dataset was incomplete. Eventually, 555 men were included in the present analysis. The study protocol was approved by the local Ethics Committee and participants gave their informed consent to participate.

Examination procedures

All examinations were performed between 0800 and 1100 h, in a quiet and comfortable room within the medical centers of the Pozzuoli and Marcianise factories, with the participants having fasted for at least 13 h. The participants were allowed to pursue their normal activities but were discouraged from engaging in vigorous exercise and were asked to abstain from smoking and from drinking alcohol, coffee, tea and other beverages containing caffeine during the morning of the study. The study included a physical examination and anthropometric measurements, a resting 12-

lead electrocardiogram, a blood test, a fasting timed urine collection and the administration of a questionnaire including information on job history, medical history, working and leisure time physical activity, dietary, drinking and smoking habits.

Protocol for the study of renal sodium handling

The participants consumed their evening meal at no later than 1900 h and took a 300 mg lithium carbonate capsule (Carbolithium, IFI, Milan, Italy) delivering 8.1 mmol of elemental lithium, at 2200 h with 400 ml of tap water. On the morning of the study, after having first voided and discarded overnight urine and consumed 400 ml of tap water, they produced a fasting timed urine collection. The collection time and volume were recorded and a specimen was used for the analysis. At the mid-point of the urine collection, a blood sample was obtained by venipuncture with the subject in the seated position and without stasis between 0800 and 1100 h. Creatinine, sodium, lithium and uric acid on serum and urine samples were measured as described below. Standard formulae were used to calculate the clearance of creatinine, sodium, lithium and uric acid. Values were expressed as fractional excretion (%), dividing the respective clearance by the clearance of creatinine, to neutralize the confounding effects of age, body mass and possibly incomplete urine collections. This protocol has been extensively validated in our laboratory, as described previously [27].

Anthropometry

Body weight and height were measured on a standard beam balance scale with an attached ruler. Body weight was measured to the nearest 0.1 kg and body height was measured to the nearest 1 cm, with subjects wearing light indoor clothing without shoes. The body mass index was calculated as weight (kg) divided by the height (m^2).

The umbilical circumference was measured at the umbilicus level with the subject standing erect with his abdomen relaxed, his arms at the sides and his feet together; the arm circumference was measured at the mid-point between the acromion and the olecranon with the arm relaxed and hanging just away from the side of the body, after marking the acromion with the arm flexed at a 90° angle. Measurements were performed to the nearest 0.1 cm, using a flexible inextensible plastic tape. The sagittal (antero-posterior) abdominal diameter (SAD) was measured using the Holtain-Kahn abdominal caliper (Holtain Ltd. Crosswell, UK) which allows a direct reading of the distance between the subject's back and the front of the subject's abdomen. With the subject in the supine position, a mark was made with a cosmetic pencil on the anterior abdomen at the midway between the right and left iliac crests. Then, the lower arm of the caliper

was inserted underneath the small of the back and the upper arm of the caliper was adjusted until it was just touching the abdomen at the level of the mid-abdominal mark, the subject resting in a relaxed position at the end of a normal expiration. The distance between the subject's back and the front of the subject's abdomen was read on the centimeter scale of the caliper to the nearest 0.1 cm. As with the subject lying on his back in the supine position, the abdominal subcutaneous fat tends to slipper along the flanks, the sagittal abdominal diameter is taken as an indirect estimate of the amount of visceral fat. This index has been validated against direct measurement of visceral fat by computerized tomography and nuclear magnetic resonance [28,29].

Subscapular and triceps skinfold thickness was measured using a Lange skinfold caliper (Beta Technology Inc., Santa Cruz, California, USA). The subscapular fold was picked-up just below the inferior angle of the scapula at 45° to the vertical. The tricipital fold was measured at the mid-point of the back of the upper arm between the tip of the olecranon and the acromion process of the scapula. The means of three repeat measurements at each site were used for the calculations.

Blood pressure measurement

After the subject had been sitting upright for at least 10 min, systolic and diastolic (phase V) blood pressure were taken three times, 2 min apart, with a random zero sphygmomanometer (Gelman Hawksley Ltd, Sussex, UK). The first reading was discarded and the average of the second and third reading was recorded for systolic and diastolic blood pressure.

Both anthropometric and blood pressure measurements were performed by professional operators who had attended training sessions for standardization of the procedures. The operator code was recorded in order to check for possible measurement biases.

Blood sampling and biochemical assays

A fasting venous blood sample was taken in the seated position without stasis between 0800 and 1000 h, after the blood pressure measurements, for determination of serum lipids, insulin, glucose, creatinine, sodium, lithium and uric acid levels. The blood specimens were immediately centrifuged and stored at -70° until analysed. Serum cholesterol, triglyceride, glucose and uric acid levels were measured with automated methods (Cobas-Mira; Roche, Italy), creatinine by the picric acid colorimetric method, serum and urinary electrolytes by atomic absorption spectrophotometry, uric acid by an enzymatic colorimetric method. Plasma insulin concentration was measured by radioimmunoassay (Insulin Lisophase; Technogenetics, Milan, Italy). Insulin

resistance was estimated by homeostasis model assessment (HOMA) using the formula: fasting plasma insulin ($\mu\text{U/ml}$) \times fasting plasma glucose (mmol/l)/22.5, as described by Matthews *et al.* [30]. Although this method does not give a direct measure of insulin-dependent glucose utilization, it has been validated against the euglycemic hyperinsulinemic clamp [31] and has no practical alternatives in large-scale epidemiological investigations.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS-PC; SPSS Inc., Chicago, Illinois, USA). As the distributions of serum glucose, triglyceride, insulin and HOMA index deviated significantly from normality, they were normalized by log transformation; log-transformed values were used in the analysis, as appropriate. Pearson linear correlation was used to detect bivariate associations between different variables. Analysis of variance (ANOVA) was used to assess differences between group means and the analysis of covariance to account for the effect of possible confounders. Cross-tabulation analysis was used to analyse the frequency of a given morbid condition across quartiles of specified anthropometric variables. Stepwise multiple linear regression was used to determine the role of different anthropometric indices as independent predictors of fractional renal tubular sodium handling allowing for potential confounders. Results are expressed as means \pm SD or 95% confidence intervals (95% CI) as indicated. Two-sided $P < 0.01$ were considered statistically significant, unless otherwise indicated.

Results

Descriptive statistics

Table 1 gives the characteristics of the study population as well as of the 261 untreated individuals who were excluded because of an incomplete dataset. The mean age of the participants in the study was 50.5 years, the majority of the population comprising middle-aged men. There were 155 participants (27.9%) with systolic pressure of 140 mmHg or above and/or diastolic pressure of 90 mmHg or above. Seventy-five participants (13.5%) had a body mass index (BMI) (kg/m^2) above 30.

The characteristics of the subgroup excluded from the analysis were comparable to those of the major group apart from a 1.5-year difference in age.

Relationship of anthropometric measures to blood pressure and insulin sensitivity

The anthropometric indices of adiposity were highly interrelated. In particular, there were strong relationships between BMI, sagittal diameter and umbilical circumference ($r =$ between 0.52 and 0.77, $P < 0.001$).

Table 1 Characteristics of the study population and of the subjects excluded from the analysis because of an incomplete data set

	Study population (n = 555)	Subjects excluded from the analysis (n = 261)
Age (years)	50.6 (7.2)	51.9 (7.8)*
Systolic blood pressure (mmHg)	126.8 (15.2)	128.2 (16.5)
Diastolic blood pressure (mmHg)	82.7 (9.1)	82.9 (9.3)
Serum glucose (mmol/l)	5.40 (0.61)	5.27 (0.55)
Serum glucose (mg/dl)	97.3 (11.0)	94.9 (10.0)
Serum cholesterol (mmol/l)	5.73 (1.06)	5.60 (0.97)
Serum cholesterol (mg/dl)	221.7 (41.0)	216.7 (37.6)
Serum trygliceride (mmol/l)	1.66 (0.91)	1.62 (0.97)
Serum trygliceride (mg/dl)	147.0 (80.3)	143.2 (86.1)
Serum uric acid (μ mol/l)	336.8 (70.4)	328.2 (67.3)
Serum uric acid (mg/dl)	5.66 (1.18)	5.52 (1.13)
Serum insulin (fasting) (pmol/l)	61.9 (43.1)	60.5 (26.7)
Serum insulin (fasting) (mU/l)	8.91 (6.20)	8.71 (3.82)
Serum creatinine (μ mol/l)	85.4 (12.1)	83.6 (10.6)
Serum creatinine (mg/dl)	0.97 (0.14)	0.95 (0.12)
Creatinine clearance (ml/min per m ²)	49.9 (15.5)	49.7 (24.6)
Body mass index (kg/m ²)	26.7 (2.9)	26.6 (3.1)
Sagittal abdominal diameter (cm)	21.1 (2.4)	21.0 (2.5)
Umbilical circumference (cm)	93.9 (8.0)	93.6 (8.7)
Subscapular skinfold thickness (mm)	20.6 (8.7)	19.7 (6.8)
Arm circumference (cm)	30.1 (2.7)	29.9 (2.9)
Tricipital skinfold thickness (mm)	16.7 (7.7)	16.3 (6.0)

* $P < 0.01$.

In univariate analysis, the BMI and the anthropometric indices of central adiposity (sagittal diameter, umbilical circumference and subscapular skinfold thickness) were significantly and directly related to both systolic and diastolic pressure (r between 0.154 and 0.248, P between < 0.01 and < 0.001). The tricipital skinfold thickness and the arm circumference were more weakly related (r between 0.075 and 0.159, P between < 0.05 and < 0.01). The indices of central adiposity were also significantly and directly associated with fasting serum insulin and with the HOMA index (r between 0.223 and 0.342, $P < 0.001$). The tricipital skinfold thickness and the arm circumference again were more weakly related (r between 0.115 and 0.162, respectively, P between < 0.05 and < 0.01).

There were direct relationships of the umbilical circumference ($r = 0.137$, $P < 0.01$) and the sagittal abdominal diameter ($r = 0.089$, $P < 0.05$) with age.

When the study population was stratified by quartile of sagittal abdominal diameter (taken as an index of central adiposity) no differences were observed between quartiles as regard to age, serum creatinine, creatinine clearance referred to body surface area and urinary sodium excretion rate, whereas a gradual increase was observed in systolic and diastolic pressure with stepwise increasing values of sagittal diameter. The systolic and diastolic pressure of participants in the upper quartile: 130 (95% CI 128–133)/86 (95% CI 84–87) were significantly higher than those of participants in the first quartile: 123 (95% CI 120–125)/80 (95% CI 79–81) mmHg, $P < 0.001$. Based on a cut-off of

140 mmHg for systolic and/or 90 mmHg for diastolic pressure, the prevalence of hypertension rose from 22.7 to 37.5% across quartiles of sagittal abdominal diameter. Pulse rate was marginally higher in men in the upper quartile (63.6 beats/min) compared with men in the first three quartiles (60.6, 60.6 and 60.9 beats/min, respectively, $F = 3.20$, $P = 0.05$).

A similar trend was apparent for the levels of metabolic variables: fasting serum insulin, HOMA index and trygliceride concentration all increased stepwise across quartiles of sagittal diameter, with mean values in the highest quartile being significantly higher than those in the two lowest quartiles ($P < 0.001$). Using a cut-off for the HOMA index of 2.77, identified in a recent study as the 80% percentile for a population of non-obese subjects with no metabolic disorder [30], the prevalence of abnormal values suggestive of insulin resistance increased from 8.8% in the lower to 37.5% in the upper quartile of sagittal abdominal diameter. Similar results were obtained if the population was stratified by BMI or by umbilical circumference, but not by arm circumference or tricipital skinfold thickness.

Relationship of renal tubular sodium handling to anthropometric measures and insulin sensitivity

The average urine collection time for the 555 participants included in the analysis was 237 ± 65 min (mean \pm SD) and the average urine volume was 420 ± 204 ml. The urinary sodium excretion rate was 153 ± 71 μ mol/min.

The fractional excretions of lithium and uric acid were directly related to each other ($r = 0.342$, $P < 0.001$). They were both significantly and inversely associated with the sagittal abdominal diameter ($r = -0.132$, $P < 0.01$ for lithium and $r = -0.128$, $P < 0.001$ for uric acid fractional excretion), the umbilical circumference ($r = -0.103$, $P < 0.05$ and $r = -0.121$, $P < 0.01$) and the BMI ($r = -0.119$, $P < 0.01$ and $r = -0.107$, $P < 0.05$). Neither the exogenous lithium, nor the uric acid fractional excretion, were associated with the arm circumference or the tricipital skinfold thickness (r between -0.007 and 0.052) or with serum insulin ($r = -0.050$). The fractional excretion of sodium was not associated with any of these anthropometric indices (r between -0.048 and -0.067). There was no statistical association between the urinary sodium excretion rate and the anthropometric indices of adiposity (r between 0.031 and 0.071).

The results of the analysis of linear regression of the fractional excretion of lithium and uric acid on measures of body mass and of fat distribution are given in Tables 2 and 3. In addition to the standard linear regression coefficients, Tables 2 and 3 give the estimated changes in the two indices of tubular sodium

Table 2 Linear regression of fractional excretion of uric acid on selected anthropometric indices (n = 555)

	Intercept (units)	Slope (units)	Δ FEUA (units) by 1 SD increase in index*	P
BMI (kg/m ²)	11.3	-0.11	-0.32	0.007
SAD (cm)	11.5	-0.15	-0.36	0.003
Umbilical circumference (cm)	12.4	-0.04	-0.35	0.004
Subscapular skinfold (mm)	8.93	-0.03	-0.23	0.054
Arm circumference (cm)	9.77	-0.05	-0.12	0.306
Tricipital skinfold (mm)	8.49	-0.01	-0.05	0.658

*Refer to Table 1 for SD values. BMI, body mass index; SAD, sagittal abdominal diameter; FEUA, fractional excretion of uric acid.

Table 3 Linear regression of fractional excretion of lithium on selected anthropometric indices (n = 555)

	Intercept (units)	Slope (units)	Δ FELi (units) by 1 SD increase in index*	P
BMI (kg/m ²)	33.6	-0.30	-0.86	0.006
SAD (cm)	34.2	-0.41	-0.97	0.002
Umbilical circumference (cm)	34.6	-0.09	-0.76	0.016
Subscapular skinfold (mm)	27.7	-0.10	-0.84	0.007
Arm circumference (cm)	29.9	-0.14	-0.38	0.229
Tricipital skinfold (mm)	26.1	-0.03	-0.21	0.508

*Refer to Table 1 for SD values. BMI, body mass index; SAD, sagittal abdominal diameter; FELi, fractional excretion of lithium.

handling by 1 SD change in each anthropometric measure, thereby making direct comparisons possible of the effects of the different measures.

The regression lines of fractional excretion of lithium and uric acid on BMI, sagittal abdominal diameter, umbilical circumference and subscapular skinfold thickness had similar slopes, indicating that their respective variations upon differences in these anthropometric measures were of similar magnitude. All the slopes were significantly different from zero indicating statistically significant variation in the fractional excretion of both lithium and uric acid with differences in central adiposity. On the other hand, no significant variation was observed in the two indices of renal sodium handling with differences in measures of peripheral adiposity (arm circumference and tricipital skinfold thickness).

To further evaluate the influence of adiposity on the fractional renal tubular sodium handling, multiple linear regression analysis was performed by setting multiple linear regression equations having the fractional excretion of uric acid or of exogenous lithium as dependent variable. BMI, sagittal abdominal diameter, umbilical and arm circumference, subscapular and tricipital skinfold thickness were introduced as independent variables in different equations, with age, blood pressure and fasting serum insulin as covariates. The results of this analysis are shown in Tables 4 and 5.

The sagittal abdominal diameter, the umbilical circumference and the BMI all entered as significant predictors of the fractional excretion of both uric acid and exogenous lithium, accounting for age, blood pressure (either systolic or diastolic) and fasting serum insulin levels. The arm circumference and the tricipital skin-

Table 4 Multiple linear regression of fractional excretion of uric acid on selected anthropometric variables (n = 555)

Equation no. and anthropometric variable tested	B (95% CI)	P
Body mass index	-0.111 (-0.192 to -0.030)	0.007
Sagittal abdominal diameter	-0.175 (-0.276 to -0.074)	0.001
Umbilical circumference	-0.050 (-0.080 to -0.020)	0.001
Subscapular circumference	-0.027 (-0.054-0.001)	0.054
Tricipital circumference	-0.011 (-0.043-0.021)	0.495
Arm circumference	-0.052 (-0.142-0.038)	0.254

Age, systolic blood pressure and fasting serum insulin concentration added to all equations as fixed covariates.

Table 5 Multiple linear regression of fractional excretion of exogenous lithium on selected anthropometric variables (n = 555)

Equation no. and anthropometric variable tested	B (95% CI)	P
Body mass index	-0.296 (-0.506 to -0.086)	0.006
Sagittal abdominal diameter	-0.406 (-0.662 to -0.150)	0.002
Umbilical circumference	-0.090 (-0.171 to -0.018)	0.016
Subscapular circumference	-0.010 (-0.167 to -0.026)	0.007
Tricipital circumference	-0.034 (-0.119-0.043)	0.359
Arm circumference	-0.148 (-0.379-0.083)	0.208

Age, systolic blood pressure and fasting serum insulin concentration added to all equations as fixed covariates.

fold thickness were not independent predictors of either uric acid or lithium fractional excretion.

Discussion

In accordance with the results of several previous studies, the analysis of this population of untreated men shows a clustering of overweight, insulin resistance and blood pressure elevation, commonly referred to as metabolic or insulin resistance syndrome [1–2,5–9]. Visceral adiposity plays a well-recognized role in this condition [1,4,5,32] and it may not be surprising that in our study population all the indices of central adiposity were significantly and directly associated with markers of insulin resistance, including fasting serum insulin, the HOMA index, fasting triglyceride and uric acid levels. Although it was not possible to perform a direct measurement of insulin sensitivity, which is a limitation common to large-scale epidemiological investigations, the HOMA index has been successfully validated against the euglycemic hyperinsulinemic clamp in a large number of subjects [30]. It was also not possible to standardize dietary carbohydrate intake prior to blood testing; nevertheless, no correlation was detected between the HOMA index and the habitual total carbohydrate intake estimated by food-frequency questionnaire ($r = -0.020$, $P = 0.645$).

Among the anthropometric indices, the sagittal abdominal diameter has been particularly well validated as an indirect measure of visceral adiposity in men by advanced technology imaging techniques [28,29,33]. In our population, the sagittal abdominal diameter was significantly and positively associated with systolic and diastolic pressure: men in the upper quartile of this measure of central adiposity were, as a group, hyperinsulinemic, insulin-resistant and hypertensive. Similar findings were obtained using the umbilical circumference as an other index of abdominal adiposity.

The most important novel finding provided by the analysis of the Olivetti dataset was that abdominal adiposity was associated with an alteration in the renal handling of exogenous lithium and uric acid. This alteration was specific for abdominal adiposity, as in both univariate and multivariate analysis no association was observed between tricipital skinfold thickness or arm circumference and the renal handling of the two substances. It might be argued that the strength of the statistical associations detected in our population was relatively low, being based in most cases on correlation coefficients between 0.10 and 0.15. However, this relative weakness is in part attributable to the regression dilution bias affecting the measurement of lithium and uric acid clearance in an epidemiological setting. Despite this limitation, the clearances of lithium and uric acid are nevertheless the best indicators of prox-

imal tubular sodium handling in clinical and population-based studies.

While sodium and water are reabsorbed at several sites along the nephron, the lithium ion, once filtered by the glomerulus, is reabsorbed largely at the proximal tubule so that the amount of substance escaping reabsorption at this level is almost quantitatively excreted in the urine. As the lithium ion is carried through the tubular epithelium by the same transport systems that drive sodium and water, a reduction in the fractional excretion of lithium argues for increased reabsorption of sodium and water at the proximal tubule [34,35]. To a good extent, similar considerations can be made for the clearance of uric acid, as urate transportation also occurs mainly in the proximal tubule along pathways linked to sodium and water reabsorption [36].

One limitation of these techniques is that they provide only indirect evidence of the proximal tubular sodium transport *in vivo*. However, micropuncture studies in animals showed that the lithium clearance provides a reasonably correct measure of the end-proximal delivery of sodium and fluid [34]. The reliability and accuracy of the protocol adopted in the present study was carefully investigated under various experimental conditions by our group, as previously reported [27]. In particular, we have shown that, at the dosage used in our protocol, exogenous lithium does not affect sodium excretion *per se* [27]. Expressing the renal clearance of lithium and uric acid as fractional excretion has the advantage of providing a measure that is independent of the glomerular filtration rate and of possible sources of bias such as differences in flow rate and incomplete urine collection.

Another potential source of bias is the lack of standardization of dietary sodium chloride intake prior to our measurements, given previous observations by our own group that markedly reduced sodium intake may reduce the fractional excretion of exogenous lithium [27]. However, we found no evidence in our study population suggesting that abdominal adiposity was associated with lower sodium intake. Instead, there was a trend to direct, though not statistically significant, correlation between measures of abdominal adiposity (i.e. the sagittal abdominal diameter and the umbilical circumference) and the urinary sodium excretion rate measured on morning timed urine collections. The same was true for the relationship between these same anthropometric indices and the habitual dietary sodium intake estimated from food-frequency questionnaire ($r = 0.061$, $P = 0.15$ and $r = 0.064$, $P = 0.17$), suggesting that, if anything, men with abdominal adiposity might have greater, not lower, sodium intake.

Our data therefore indicate that central adiposity is

associated with a significantly enhanced rate of tubular sodium reabsorption at one or more proximal site(s), independently of sodium intake and blood pressure. This finding is in keeping with previous reports in humans, as well as in dogs, suggesting that obesity-induced hypertension is associated with impaired pressure natriuresis [37–39].

Several mechanisms might be responsible for enhanced tubular sodium reabsorption in relation to central adiposity. Tubular sodium reabsorption depends on the activity of ion transport systems that are modulated by neural, endocrine, paracrine and physical factors. An important factor is insulin, which has an acute antinatriuretic effect [15–16], also shared by obese individuals despite concomitant resistance to other metabolic effects of the hormone [40]. However, in multivariate regression analysis in our study, the relationship of the fractional excretion of lithium and uric acid to abdominal adiposity was independent of fasting serum insulin concentration; moreover, insulin was not a significant predictor of these two markers of proximal tubular sodium handling. These results are in keeping with those by Ter Maaten *et al.* [16] who showed, using the lithium clearance technique in healthy volunteers, that the sodium-retaining effect of acute hyperinsulinemia was probably exerted at a site beyond the proximal tubule. Accordingly, our findings do not support a role for hyperinsulinemia in the enhanced rate of tubular sodium reabsorption in the renal proximal tubule.

Sympathetic nerve activity is another factor that influences the renal tubular handling of sodium. Obesity induced by a high-fat, high-calorie diet in the dog is associated with sympathetic activation and a NaCl-dependent form of hypertension [13], which is attenuated by concomitant administration of clonidine [14]. In humans, evidence of enhanced sympathetic tone in the obese state has been found in many [41–43], though not all [44] studies. In the Olivetti study population, pulse rate, an approximate marker of intersubject differences in sympathetic tone [45], was marginally higher in subjects with greater abdominal adiposity.

A role of alterations in intrarenal physical forces in the enhanced tubular sodium and water reabsorption observed in obesity is supported by evidence from animal experiments [12]: whether this may occur in humans with visceral adiposity is not known.

Whatever the mechanism(s), it is plausible that the renal tubular abnormality in sodium handling observed in men with central adiposity could contribute to raise blood pressure in predisposed individuals living in a high salt environment, by shifting the pressure–natriur-

esis curve to the right, thus making higher blood pressures necessary to excrete a given sodium load.

Some limitations of the present work are inherent to the nature of the Olivetti study cohort, which comprised white male participants only and thus may not be regarded as representative of the general population. For this reason, the results of this study can be only generalized to a comparable white male population. Given the relatively large prevalence of obese individuals, it is also possible that, despite the exclusion of subjects with a fasting blood glucose value beyond 7.7 mmol/l (or 126 mg/dl), some diabetic subjects may have been left in the population analysed.

In conclusion, our findings are relevant to the prevention of the cardiovascular sequels of obesity in as much as they suggest a possible mechanistic link between abdominal adiposity and increased risk of hypertension and provide a plausible explanation for the finding of salt-sensitivity in obese individuals.

Acknowledgements

The authors are grateful to Dr Umberto Candura, Dr Antonio Scottoni and Ms Maria Bartolomei, in charge of the Olivetti factory medical center, for their valuable collaboration in the organization and coordination of the study in the field. They also thank the Olivetti employees for their enthusiastic participation. The excellent cooperation of Dr Eliana Ragone and Dr Francesco Stinga in the work in the field and of Ms Elisabetta Della Valle for laboratory help is gratefully recognized. The editorial assistance of Ms Rosanna Scala for linguistic revision and Ms Grazia Fanara for preparation of the manuscript are also gratefully acknowledged.

References

- 1 Johnson D, Prud'homme D, Després J-P, Nadeau A, Tremblay A, Bouchard C. Relation of abdominal obesity to hyperinsulinemia and high blood pressure in men. *Int J Obes* 1992; **16**:881–890.
- 2 Croft JB, Strogatz DS, Keenan NL, James SA, Malarcher AM, Garrett JM. The independent effects of obesity and body fat distribution on blood pressure in black adults: The Pitt County study. *Int J Obes* 1993; **17**:391–397.
- 3 Folsom AR, Prineas RJ, Kaye SA, Munger RG. Incidence of hypertension and stroke in relation to body fat distribution and other risk factors in older women. *Stroke* 1990; **21**:701–706.
- 4 Marin P, Andersson B, Ottosson M, Olbe L, Chowdhury B, Kvist H, *et al.* The morphology and metabolism of intraabdominal adipose tissue in men. *Metabolism* 1992; **41**:1242–1248.
- 5 Toft I, Bonaa KH, Jenssen T. Insulin resistance in hypertension is associated with body fat rather than blood pressure. *Hypertension* 1998; **32**:115–122.
- 6 Rosmond R, Bjorntorp P. Blood pressure in relation to obesity, insulin and the hypothalamic-pituitary-adrenal axis in Swedish men. *J Hypertens* 1998; **16**:1721–1726.
- 7 Daniels SR, Morrison JA, Sprecher DL, Khoury P, Kimball TR. Association of body fat distribution and cardiovascular risk factors in children and adolescents. *Circulation* 1999; **99**:541–545.
- 8 Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M. Hyperinsulinemia. A link between hypertension, obesity and glucose intolerance. *J Clin Invest* 1985; **75**:809–817.

- 9 Ferrannini E, Buzzigoli G, Bonadonna R, Glorico MA, Oleggini M, Graziadei L. Insulin resistance in essential hypertension. *N Engl J Med* 1987; **317**:350–357.
- 10 Pollare T, Lithell H, Berne C. Insulin resistance is a characteristic feature of primary hypertension independent of obesity. *Metabolism* 1990; **39**:167–174.
- 11 Reaven GM. Insulin resistance and compensatory hyperinsulinemia: role in hypertension, dislipidemia, and coronary heart disease. *Am Heart J* 1991; **121**:1283–1288.
- 12 Hall JE. Renal and cardiovascular mechanisms of hypertension in obesity. *Hypertension* 1994; **23**:381–394.
- 13 Kassab S, Kato T, Wilkins FC, Chen R, Hall JE, Granger JP. Renal denervation attenuates the sodium retention and hypertension associated with obesity. *Hypertension* 1995; **25**:893–897.
- 14 Rocchini AP, Mao HZ, Babu K, Marker P, Rocchini AJ. Clonidine prevents insulin resistance and hypertension in obese dogs. *Hypertension* 1999; **33**:548–553.
- 15 DeFronzo RA. The effect of insulin on renal sodium metabolism. *Diabetologia* 1981; **21**:165–171.
- 16 Ter Maaten JC, Voorburg A, Heine RJ, Ter Wee PM, Donker AJ, Gans RO. Renal handling of urate and sodium during acute physiological hyperinsulinemia in healthy subjects. *Clin Sci* 1997; **92**:51–58.
- 17 Campese VM. Salt-sensitive hypertension: cardiovascular and renal implications. *Nutr Metab Cardiovasc Dis* 1999; **9**:143–156.
- 18 Rocchini AP, Katch V, Kveselis D, Moorehead C, Martin M, Lampman R, et al. Insulin and renal sodium retention in obese adolescents. *Hypertension* 1989; **14**:367–374.
- 19 Skott P, Vaag A, Buunt NE, Hother-Nielsen O, Beck-Nielsen H, Parving H-H. Effect of insulin on renal sodium handling in hyperinsulinemic type 2 diabetic patients with peripheral insulin resistance. *Diabetologia* 1991; **34**:275–281.
- 20 Shimamoto K, Hirata A, Fukuoka M, Higashiura K, Miyazaki Y, Shiiki M, et al. Insulin sensitivity and the effects of insulin on renal sodium handling and pressor systems in essential hypertensive patients. *Hypertension* 1994; **23** (suppl):129–133.
- 21 Rocchini AP. Role of obesity in the association of insulin resistance and salt sensitivity of blood pressure. *Nutr Metab Cardiovasc Dis* 1997; **7**:132–137.
- 22 Cappuccio FP, Strazzullo P. Altered renal tubular sodium handling: a new feature of the insulin resistance syndrome? *Nutr Metab Cardiovasc Dis* 1997; **7**:142–145.
- 23 Simsolo RB, Romo MM, Rabinovich L, Bonanno M, Grunfeld B. Family history of essential hypertension versus obesity as risk factors for hypertension in adolescents. *Am J Hypertens* 1999; **12**:260–263.
- 24 Dengel DR, Hogikyan RV, Brown MD, Glickman SG, Supiano MA. Insulin sensitivity is associated with blood pressure response to sodium in older hypertensives. *Am J Physiol* 1998; **274**:E403–E409.
- 25 Cappuccio FP, Strazzullo P, Siani A, Trevisan M. Increased proximal sodium reabsorption is associated with increased cardiovascular risk in men. *J Hypertens* 1996; **14**:909–914.
- 26 Cappuccio FP, Strazzullo P, Farinano E, Trevisan M. Uric acid metabolism and tubular sodium handling: results from a population-based study. *JAMA* 1993; **270**:354–359.
- 27 Strazzullo P, Iacoviello L, Iacone R, Giorgione N. The use of fractional lithium clearance in clinical and epidemiological investigation: a methodological assessment. *Clin Sci* 1988; **74**:651–657.
- 28 Kvist H, Chowdhury B, Grangard U, Tylén U, Sjöström L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. *Am J Clin Nutr* 1988; **48**:1351–1361.
- 29 van der Kooy K, Leenen R, Seidell JC, Deurenberg P, Visser M. Abdominal diameters as indicators of visceral fat: comparison between magnetic resonance imaging and anthropometry. *Br J Nutr* 1993; **70**:47–58.
- 30 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner AC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**:412–419.
- 31 Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. *Diabetes* 1998; **47**:1643–1649.
- 32 Macor C, Ruggeri A, Mazzonetto P, Federspil G, Cobelli C, Vettor R. Visceral adipose tissue impairs insulin secretion and insulin sensitivity but not energy expenditure in obesity. *Metabolism* 1997; **46**:123–129.
- 33 Van der Kooy K, Leenen R, Seidell JC, Deurenberg P, Droop A, Bakker GJG. Waist-hip ratio is a poor predictor of changes in visceral fat. *Am J Clin Nutr* 1993; **57**:327–333.
- 34 Boer WH, Fransen R, Shirley DG, Walter SJ, Boer P, Koomans HA. Evaluation of the lithium clearance method: Direct analysis of tubular lithium handling by micropuncture. *Kidney Int* 1995; **47**:1023–1030.
- 35 Boer WH, Koomans HA, Beutler JJ, Gaillard CA, Rabelink AJ, Dorhout Mees EJ. Small intra- and large inter-individual variability in lithium clearance in humans. *Kidney Int* 1989; **35**:1183–1188.
- 36 Kahn AM. Indirect coupling between sodium and urate transport in the proximal tubule. *Kidney Int* 1989; **36**:378–384.
- 37 Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, et al. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med* 1989; **321**:580–585.
- 38 Hall JE, Brands MW, Dixon WN, Smith MJ Jr. Obesity-induced hypertension: renal function and systemic hemodynamics. *Hypertension* 1993; **22**:292–299.
- 39 Granger JP, West D, Scott J. Abnormal pressure natriuresis in the dog model of obesity-induced hypertension. *Hypertension* 1994; **23** (suppl):8–111.
- 40 Rocchini AP. The relationship of sodium sensitivity to insulin resistance. *Am J Med Sci* 1994; **307** (suppl 1):S75–S80.
- 41 Tuck ML. Obesity, the sympathetic nervous system, and essential hypertension. *Hypertension* 1992; **19**:167–177.
- 42 Young JB, Landsberg L. Diet-induced changes in sympathetic nervous system activity: possible implications for obesity and hypertension. *J Chron Dis* 1982; **35**:879–886.
- 43 Grassi G, Seravalle G, Dell'Oro R, Bolla GB, Mancia G. Adrenergic and reflex abnormalities in obesity-related hypertension. *Hypertension* 2000; **36**:538–542.
- 44 Tataranni PA, Young JB, Bogardus G, Ravussin E. A low sympathoadrenal activity is associated with body weight gain and development of central adiposity in Pima Indian men. *Obes Res* 1997; **5**:341–347.
- 45 Grassi G, Vailati S, Bertinieri G, Seravalle G, Stella ML, Dell'Oro R, Mancia G. Heart rate as marker of sympathetic activity. *J Hypertens* 1998; **16**:1635–1639.