Abnormalities of renal sodium handling in the metabolic syndrome. Results of the Olivetti Heart Study

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Objective The mechanisms underlying high blood pressure in the framework of metabolic syndrome (MS) are not clarified: we thus analyzed the relationship of MS and its components to renal tubular sodium handling among participants of the Olivetti Heart Study, an epidemiological investigation of a representative sample of adult white male population in southern Italy.

Methods Proximal (FPRNa) and distal (FDRNa) fractional sodium reabsorption were estimated by the clearance of exogenous lithium in 702 participants aged 25–75 years examined in 1994–1995. Blood pressure and relevant anthropometric and biochemical variables were also measured. The diagnosis of MS was based on modified National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATP III) criteria.

Results FPRNa, but not FDRNa, was directly associated with body mass index (BMI), waist circumference, diastolic pressure, serum triglyceride and uric acid, independently of age and of antihypertensive treatment. After adjustment for age, FPRNa, but not FDRNa, was significantly greater in individuals with MS, as compared to those without [77.6% (95% confidence interval = 76.7–80.1) versus 74.4% (73.7–75.1), $P < 0.001$]. A similar difference was observed after the exclusion of participants on current antihypertensive treatment ($P = 0.018$). In untreated individuals, a significant interaction was observed between obesity and insulin resistance as related to FPRNa ($P = 0.002$): the highest age-adjusted levels of FPRNa were detected in obese hypertensive and obese insulin-resistant participants.

Conclusion In this sample of an adult male population, MS was associated with an increased rate of FPRNa. This finding is relevant to the pathophysiology of MS and possibly to the prevention of its cardiovascular and renal consequences. *J Hypertens* 24:1633–1639 © 2006 Lippincott Williams & Wilkins.

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Introduction

The study of renal segmental tubular sodium handling by measurement of exogenous or endogenous lithium clearance has been a source of valuable information about in-vivo alterations of tubular sodium and water transport in humans [1–3]. This technique is based on the principle that, while sodium and water are reabsorbed at several sites along the nephron, the lithium ion is taken up almost exclusively at proximal tubular sites, so that the amount of lithium escaping reabsorption at this level is quantitatively excreted in the urine. As lithium in the proximal tubule is transported by the same systems driving sodium and water, the parallel measurement of lithium, sodium and creatinine clearance may provide reasonably accurate and complete information as to the occurrence of abnormalities in sodium and water handling at different sites along the nephron [3].

In both normotensive and hypertensive volunteers, it was found that salt-sensitive individuals had impaired modulation of fractional proximal sodium reabsorption upon switching from a low-sodium to a sodium-rich diet [4,5], suggesting that proximal tubular sodium handling is an important determinant of the alteration in the pressure–natriuresis relationship occurring in patients with salt-sensitive hypertension. Furthermore, alterations in renal sodium handling have been associated with abdominal adiposity, another component of the so-called metabolic syndrome (MS) in previous limited analyses of the Olivetti Heart Study population examined in 1987 [1]

and in 1994–1995 [6]. More recently, similar alterations have been described among Caucasian participants of the Wandsworth Heart and Stroke Study [7]. These observations are conceptually in keeping with other findings suggesting an abnormal pressure–natriuresis relationship [8] and an increased salt-sensitivity of blood pressure [9] in obese individuals.

Since the Olivetti Heart Study provides the largest Caucasian population sample in which a standardized investigation of renal segmental tubular sodium handling has been performed, we have now carried out a systematic analysis of the study database to test the hypothesis that MS is associated with alterations of renal sodium handling, and to define the site(s) along the nephron at which these alterations occur. This analysis may help to generate working hypotheses about the pathogenic role of abnormalities in renal sodium handling in relation to the development and/or maintenance of high blood pressure in this particular condition.

Methods
Study population
Seven hundred and eighteen unselected men in the age range 25–75 years, participating in the 1994–1995 examination of the Olivetti Heart Study, gave their consent to undertake the lithium clearance protocol. The methodology of the study has been described in detail elsewhere [2,6]. The study protocol was approved by the local ethics committee.

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, ltaly), 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, discarded overnight urine and consumed 400 ml of 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. Creatinine, sodium and lithium in serum and urine samples were measured by the picric acid colorimetric method and by atomic absorption spectrophotometry, respectively, and were used to estimate the renal clearance of each substance, as described previously [2,6]. The fractional excretion of sodium and lithium were calculated as the ratio of sodium or lithium clearance and creatinine clearance ($\times$ 100). While creatinine clearance was taken as an estimate of glomerular filtration rate (GFR), the use of fractional excretion of sodium and lithium allowed us to neutralize the confounding effects of age, body mass and possibly incomplete urine collections on the evaluation of segmental tubular sodium handling. The fractional excretion of sodium and lithium

were eventually used to calculate the fractional reabsorption of sodium at the proximal (FPRNa) and distal (FDRN) tubular level, according to standard formulae [3]. This lithium clearance protocol has been extensively validated, as described previously [10,11].

Blood pressure, anthropometrics and metabolic markers
After the subject had been sitting upright for at least 10 min, systolic and diastolic (phase V) blood pressure (BP) 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 readings was recorded for systolic and diastolic BP. Hypertension was defined as a BP $\geq$ 140 and/or 90 mmHg, or current antihypertensive treatment.

Body weight, height and waist circumference were measured as described [6]. The body mass index (BMI) was calculated as weight (kg) divided by the height squared (m^2). The waist circumference was taken as an index of abdominal adiposity. This index has been validated against direct measurement of visceral fat by computed tomography and nuclear magnetic resonance [12,13]. Both anthropometric and BP measurements were performed by professional operators who had attended training sessions for standardization of the procedures. Overweight was defined as a BMI $\geq$ 25 kg/m^2 and obesity as a BMI $\geq$ 30 kg/m^2. Abdominal adiposity was given by a waist circumference value $\geq$100 cm.

A fasting venous blood sample was also obtained for determination of serum glucose, total cholesterol and triglyceride, uric acid, insulin, creatinine, sodium and lithium concentration. The blood specimens were immediately centrifuged and stored at $-70°$C until analyzed. Serum cholesterol, triglyceride, glucose and uric acid levels were measured with automated methods (Cobas-Mira; Roche, Milan, Italy). Serum insulin concentration was measured by radioimmunoassay (Insulina Lisophase; Technogenetics, Milan, Italy) and urinary uric acid by an enzymatic colorimetric method. Insulin sensitivity was estimated by homeostasis model assessment (HOMA) using the formula: fasting plasma insulin (μU/ml) $\times$ fasting plasma glucose (mmol/l)/22.5, as described by Matthews *et al.* [14]. Although this method does not give a direct measure of insulin-dependent glucose utilization, it has been validated against the euglycemic hyperinsulinemic clamp as a reasonably accurate way to estimate insulin resistance [15].

Hypertriglyceridemia was defined as a serum triglyceride concentration $\geq$ 2.26 mmol/l and hyperglycemia as a fasting blood glucose level $\geq$ 6.11 mmol/l. A HOMA index $>$ 2.77, previously identified as the 80th percentile for a population of non-obese subjects with no metabolic

disorder [15], was taken as a cut-off value for the definition of insulin resistance.

Diagnosis of metabolic syndrome

The diagnosis of MS was based on the Adult Treatment Panel (ATP) III criteria [16]. However, as the measurement of serum high-density lipoprotein (HDL)-cholesterol level was not available in our study population, a positive diagnosis of metabolic syndrome was made only if at least three of the other four components of the syndrome (waist circumference ≥ 102 cm, serum triglyceride ≥ 1.69 mmol/l, fasting glucose ≥ 5.55 mmol/l or known type 2 diabetes, blood pressure ≥ 130 and/or 85 mmHg or current antihypertensive treatment) were present in a given participant. On the other hand, a negative diagnosis was made in those cases in which only one or none of these components were present, allowing for the possibility of an HDL-cholesterol level in the abnormal range. The possibility of a falsely negative diagnosis was thus eliminated. The subjects ($n = 191$) in which only two elements of the ATP III criteria were present were not included in this particular analysis.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS-PC version 11; 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.

Analysis of variance (ANOVA) was used to assess differences between group means. Multiple linear regression analysis or analysis of covariance were used to evaluate the relationship of various components of MS to FPRNa and FDRNa, adjusting for confounders. Results are expressed as means ± standard deviation (SD) or 95% confidence intervals (95% CI), as specified. In relation to the number of comparisons being performed, only two-sided P values of 0.01 or less accepted to indicate statistical significance, unless otherwise indicated.

Complete data about segmental renal sodium handling and most other variables were available for 702 participants, but blood samples for determination of serum insulin concentration were available only for 641 individuals. The main demographic, anthropometric and metabolic features of the subjects for whom serum insulin values were not available were comparable to those of the whole study population (Appendix 1).

Results

The main characteristics and the prevalence of selected metabolic abnormalities and other relevant conditions in the study population are given in Table 1 and Table 2. A high prevalence of overweight and obesity were observed. Abdominal adiposity was common. Almost 40% of the participants were hypertensive and 16% were on regular antihypertensive drug therapy prescribed by their physicians.

FPRNa and FDRNa were normally distributed. Both were directly and significantly associated with age. FPRNa was also directly associated with BMI, waist circumference, systolic and diastolic BP, serum triglyceride and uric acid, whereas no significant association was observed with fasting serum glucose, serum insulin concentration and HOMA index (Table 3). After adjustment for age, these associations were all maintained except the one between FPRNa and systolic blood pressure. If current antihypertensive treatment was also accounted for, statistically significant associations of FPRNa were maintained with BMI, serum triglyceride and uric acid.

A positive diagnosis of MS was made in 90 and a negative diagnosis in 421 study participants. As shown in Table 4, FPRNa was significantly greater in individuals with, as compared to individuals without, MS after accounting for age ($P < 0.001$), whereas no between-group difference was detected with regard to FDRNa ($P = 0.844$). MS was also associated with greater creatinine clearance [97.1

Table 1 Anthropometric and metabolic characteristics of the study population ($n = 702$)

	Mean (95% CI)
Age (years)	50.4 (50.9–52.0)
BMI (kg/m^2)	26.9 (26.7–27.1)
Waist circumference (cm)	94.5 (93.9–95.1)
Systolic blood pressure (mmHg)	129.6 (128.4–130.8)
Diastolic blood pressure (mmHg)	84.0 (83.3–84.7)
Serum glucose (mmol/l)	5.67 (5.56–5.78)
HOMA index[a]	2.0 (1.9–2.1)
GFR (creatinine clearance, ml/min)	89.9 (87.7–92.0)
Fractional proximal Na reabsorption (%)	75.1 (74.6–75.7)
Fractional distal Na reabsorption (%)	95.0 (94.8–95.1)
	n (%)
BP treatment	112 (16.0)

BMI, body mass index; HOMA, homeostasis model assessment; GFR, glomerular filtration rate; BP, blood pressure; CI, confidence interval. [a]$n = 641$.

Table 2 Prevalence of specified metabolic abnormalities in the study population ($n = 702$)

	N	%
Overweight	516	73.5
Obesity	109	15.5
Abdominal adiposity	139	19.8
Hypertension	276	39.4
Hyperglycemia	117	16.7
Insulin resistance[a]	170	26.5
Hypertriglyceridemia	142	20.3
Obesity + hypertension	67	9.6
Obesity + insulin resistance[a]	49	7.1
Insulin resistance + hypertension[a]	96	14.1

[a]$n = 641$.

Table 3 Proximal (FPRNa) and distal fractional sodium reabsorption (FDRNa) and specified variables: Pearson correlation coefficients (*n* = 702)

Variable	FPRNa (%)			FDRNa (%)		
	Crude	Age adjusted	Age and antihypertensive treatment adjusted	Crude	Age adjusted	Age and antihypertensive treatment adjusted
Age (years)	0.122*	–	–	−0.091	–	–
BMI (kg/m^2)	0.143*	0.135*	0.116*	0.002	0.010	−0.001
Waist (cm)	0.136*	0.113*	0.093	0.001	0.019	0.008
Systolic BP (mmHg)	0.115*	0.077	0.031	−0.091	−0.062	−0.092
Diastolic BP (mmHg)	0.140*	0.121*	0.083	−0.067	−0.052	−0.077
Serum glucose (mmol/l)	0.077	0.046	0.035	−0.026	−0.015	−0.021
Serum triglycerides (mmol/l)[a]	0.116*	0.109*	0.113*	−0.031	−0.026	−0.026
Uric acid (μmol/l)	0.207*	0.205*	0.189*	−0.005	0.001	−0.009
Serum insulin (pmol/l)[a]	0.018	0.016	−0.001	0.045	0.046	0.038
HOMA index[a]	0.038	0.028	0.011	0.021	0.029	0.022

Serum insulin and homeostasis model assessment (HOMA) index: *n* = 641. BMI, body mass index; BP, blood pressure. [a]log-transformed for analysis. *$P < 0.005$.

(95% CI = 91.1–103.1) versus 89.2 ml/min (86.5–92.0); $P = 0.020$] and a slightly lower fractional excretion of sodium [1.10 (95% CI = 1.00–1.20) versus 1.24% (1.19–1.28); $P = 0.020$].

Thirty-three individuals in the group with a positive diagnosis and 35 in the group with a negative diagnosis of MS were currently taking antihypertensive drugs. Overall, in comparison with untreated individuals, these subjects had a significantly greater rate of FPRNa [78.4 (95% CI = 76.7–80.1) versus 74.4% (73.7–75.1); $P < 0.001$]. They were also significantly older [54.8 (95% CI = 53.0–56.6) versus 50.4 years (49.7–51.1); $P < 0.001$] and had higher systolic blood pressure despite being on treatment [148.3 (95% CI = 144.5–152.2) versus 124.6 mmHg (123.3–126.0); $P < 0.001$]. Thus, the evaluation of segmental renal sodium handling in relation to MS was also separately made in untreated and treated participants (Table 4). The absolute difference in FPRNa between subjects with or without MS was similar among untreated and treated subgroups. This difference maintained statistical significance among untreated participants, while statistical significance was lost among treated individuals, due to the smaller sample size. Moreover, among untreated individuals the subjects with MS had a slightly, though not statistically significantly, greater creatinine clearance (Table 4).

Linear regression analysis was used to evaluate the influence of the individual components of MS on FPRNa and FDRNa accounting for age. To rule out possible confounding by concomitant antihypertensive treatment, this analysis was carried out in untreated participants only. Because of the high collinearity between the MS components, each factor was separately introduced in a multiple linear regression equation with age as a covariate. To allow a comparative evaluation of the effects of the different factors on renal tubular sodium handling, Z scores were calculated for each factor and used for the analysis. A summary report of the results is given in Table 5. BMI and waist circumference were the two factors that appeared to influence FPRNa to a significant extent. Diastolic BP was the only other component exerting a marginal influence on FPRNa. On the other hand, none of the factors evaluated affected FDRNa, with the exception of systolic BP which played a marginally significant negative effect, namely the higher the systolic BP the lower the FDRNa.

The analysis of covariance was used to detect possible interactions between the effects of the various components of MS on renal tubular sodium handling. The only significant interaction observed was that between BMI and HOMA index as related to FPRNa ($F = 9.68$; $P = 0.002$). In accordance with this finding, Table 6

Table 4 Age-adjusted differences in proximal (FPRNa) and distal fractional sodium reabsorption (FDRNa) and creatinine clearance (GFR) between participants with or without the metabolic syndrome. Values are means (95% confidence intervals)

	With metabolic syndrome	Without metabolic syndrome	*P*
All participants	*n* = 90	*n* = 421	
FPRNa (%)	77.6 (76.1–79.2)	74.4 (73.7–75.1)	0.001
FDRNa (%)	94.9 (94.5–95.3)	95.0 (94.8–95.2)	0.844
GFR (ml/min)	97.1 (91.1–103.1)	89.2 (86.5–92.0)	0.020
Untreated participants	*n* = 57	*n* = 386	
FPRNa (%)	76.6 (74.7–78.6)	74.1 (73.4–74.7)	0.018
FDRNa (%)	94.7 (94.1–95.2)	95.0 (94.8–95.2)	0.193
GFR (ml/min)	96.3 (88.7–103.8)	89.7 (86.9–92.6)	0.114
Participants on current antihypertensive treatment	*n* = 33	*n* = 35	
FPRNa (%)	79.6 (77.1–82.0)	77.2 (74.8–79.6)	0.171
FDRNa (%)	95.4 (94.6–96.1)	94.6 (93.9–95.3)	0.125
GFR (ml/min)	96.7 (87.1–106.3)	85.4 (76.1–94.7)	0.097

Table 5 Linear regression of proximal (FPRNa) and distal fractional sodium reabsorption (FDRNa) on individual components[a] of metabolic syndrome (accounting for age) in untreated participants (*n* = 588)

	FPRNa (%) β (95% CI)	*P*	FDRNa (%) β (95% CI)	*P*
BMI	1.021 (0.405 to 1.637)	<0.001	−0.023 (−0.190 to 0.145)	0.790
Waist circumference	0.797 (0.178 to 1.416)	0.012	0.012 (−0.156 to 0.179)	0.892
Glucose	0.460 (−0.127 to 1.047)	0.124	−0.045 (−0.203 to 0.113)	0.576
HOMA index[b]	0.094 (−0.626 to 0.814)	0.798	0.151 (−0.041 to 0.343)	0.124
Serum triglyceride	0.496 (−0.128 to 1.120)	0.119	−0.098 (−0.266 to 0.070)	0.254
Systolic blood pressure	0.340 (−0.376 to 1.055)	0.352	−0.196 (−0.388 to −0.004)	0.045
Diastolic blood pressure	0.636 (−0.025 to 1.297)	0.059	−0.144 (−0.322 to 0.035)	0.114

BMI, body mass index; HOMA, homeostasis model assessment; CI, confidence interval. [a]The variables are expressed as Z score. [b]*n* = 536.

Table 6 Age-adjusted proximal (FPRNa) and distal fractional sodium reabsorption (FDRNa) by insulin resistance in untreated obese participants (*n* = 69)

		FPRNa			FDRNa		
		Mean (95% CI)	*F*	*P*	Mean (95% CI)	*F*	*P*
Insulin resistance	Yes (*n* = 30)	79.0 (77.0–81.0)	6.134	0.016	95.0 (94.3–95.7)	0.123	0.727
	No (*n* = 39)	75.7 (74.0–77.5)			94.8 (94.2–95.5)		

CI, confidence interval.

shows that FPRNa was significantly greater in obese individuals with insulin resistance as compared to those without, after accounting for age.

Discussion

The analysis of this sample of an adult male population displayed a statistically significant association between MS and an important alteration of renal tubular sodium handling. Participants who were affected by MS had a significantly higher rate of sodium and water reabsorption at the proximal tubular level, independently of age. On the other hand, the rate of distal sodium reabsorption was not significantly related to the presence of MS.

Other features of the group with MS were a slight but significantly lower fractional excretion of sodium and an equally slight but significantly greater creatinine clearance. By definition, individuals with MS have higher blood pressure levels as compared with those unaffected. Thus, our findings suggest that in subjects with MS a greater avidity of the renal proximal tubule for sodium is compensated for by relative hyperfiltration, which is sustained, at least in part, by higher systemic blood pressure. These findings are in accordance with the results of a recent study on a sample of a Caucasian population in England [7]. They are also in keeping with previous demonstrations of an altered modulation of FPRNa in relation to salt sensitivity in both normotensive [4] and hypertensive individuals [5].

Many hypertensive participants were on current antihypertensive treatment in our study and, indeed, the prevalence of MS was disproportionately higher among treated individuals, raising the question that treatment itself might have contributed to a number of such cases. Nevertheless, separate analyses of renal sodium handling in relation to MS in treated and untreated participants confirmed that the rate of proximal sodium reabsorption was significantly higher in untreated participants, thus ruling out the possibility that ongoing pharmacological therapy could have been responsible for our main finding.

Separate analyses of the relationships of the single components of MS to renal sodium handling were also carried out with adjustment for age. The use of the Z scores of the single variables allowed a quantitative comparison of their effect on the rates of proximal and distal tubular sodium reabsorption. Our results indicated that, apart from age, body mass index and abdominal adiposity exerted a greater and statistically significant influence on FPRNa. It may be speculated that one of the reasons for the rise in the rate of proximal tubular sodium reabsorption with age is the body weight gain and abdominal fat accumulation commonly associated with aging, particularly in males. In fact, partial correlation analysis showed a sizable reduction in the strength of the correlation between FPRNa and age after adjustment for waist circumference (correlation coefficient decreases from 0.121 to 0.100).

FPRNa was also directly associated with serum triglyceride and serum uric acid, again independently of age. Higher levels of both triglyceride and uric acid are often found with excess abdominal adiposity and, together with abdominal fat deposition, are common features of MS [17]. While in absolute terms the associations observed are to be classified as low-order correlations, their relative weakness may be explained in part by the substantial regression dilution bias affecting the

measurement of many of the variables involved in an epidemiological setting.

The lack of statistically significant associations between FPRNa, serum glucose, serum insulin concentration and HOMA index are somewhat surprising given the association between FPRNa and the other features of the metabolic syndrome. One reasonable explanation for this unexpected finding might be the regression dilution bias affecting the measurement of both serum glucose and insulin concentration. This interpretation is supported by the significant interaction detected in the relationship of BMI and HOMA index with FPRNa in our study population. Indeed, this observation led us to examine the relationship between insulin resistance and FPRNa separately in obese and non-obese individuals. This analysis indicated that in obese subjects insulin resistance is actually associated with a higher rate of FPRNa, whereas no such relationship is observed in the non-obese population. In other words, when the alteration in serum insulin level and insulin resistance is more marked (as in frankly obese individuals), their association with altered tubular sodium handling becomes apparent. Indeed, the highest values of fractional proximal sodium reabsorption were detected in obese individuals with insulin resistance. Although conclusions about cause–effect relationships cannot be drawn from epidemiological observations, this finding is compatible with the hypothesis that increased serum insulin levels could play a role in the alteration of renal sodium handling found in obese individuals, possibly through the stimulation of sympathetic activity [18,19]. It may also be speculated that elevated plasma leptin concentrations, as those found in obese insulin-resistant individuals, might contribute to the increase in tubular sodium and water reabsorption through sympathetic renal nerve stimulation [20,21].

A limitation of the present work is that the Olivetti study cohort was made of Caucasian male participants only: its results may thus be generalized only to a comparable Caucasian male populations. Another limitation was the lack of measurement of HDL-cholesterol, an important component of MS. This may have produced some difference in the characteristics of the subjects diagnosed as having MS based on the criteria used in our study as compared to the proper NCEP-ATP III definition; it seems, however, very unlikely that this problem may affect the interpretation of our findings.

Overall, our results indicate that an alteration of renal tubular sodium handling is an important feature of MS, involving an increased rate of proximal sodium and water reabsorption with a modification of the normal pressure–natriuresis relationship. These findings are relevant to the pathophysiology of MS and also possibly to the prevention of its cardiovascular and renal consequences.

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Appendix

Anthropometric and metabolic characteristics of participants with or without serum insulin determination

	With ($n = 641$)	Without ($n = 61$)	P
BP treatment [n (%)]	103 (16.1)	9 (14.8)	0.476
Age (years)	51.6 (51.1–52.2)	49.0 (47.8–50.3)	0.008
BMI (kg/m^2)	26.9 (26.7–27.1)	25.9 (26.7–27.7)	0.821
Waist circumference (cm)	94.5 (93.9–95.2)	94.1 (91.8–96.4)	0.675
Systolic blood pressure (mmHg)	129.8 (128.5–131.1)	127.3 (123.7–130.9)	0.257
Diastolic blood pressure (mmHg)	84.0 (83.2–84.8)	84.2 (82.1–86.3)	0.873
Serum glucose (mmol/l)	5.66 (5.55–5.77)	5.55 (5.11–5.94)	0.460
Fractional proximal Na reabsorption (%)	75.1 (74.5–75.6)	76.2 (74.3–77.7)	0.329
Fractional distal Na reabsorption (%)	95.0 (94.8–95.1)	95.0 (94.8–95.1)	0.939

For all characteristics except blood pressure (BP) treatment, values are means (95% confidence interval). BMI, body mass index; Na, sodium.