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The effect of a shift in sodium intake on renal hemodynamics is determined by body mass index in healthy young men

JA Krikken¹, AT Lely¹, SJL Bakker¹ and G Navis¹

¹Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

A body mass index (BMI) ≥ 25 kg/m² increases the risk for long-term renal damage, possibly by renal hemodynamic factors. As epidemiological studies suggest interaction of BMI and sodium intake, we studied the combined effects of sodium intake and BMI on renal hemodynamics. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured in 95 healthy men (median age 23 years (95% confidence interval: 22–24), BMI: 23.0 ± 2.5 kg/m²) on low (50 mmol Na⁺, LS) and high (200 mmol Na⁺, HS) sodium intake. Mean GFR and ERPF significantly increased by the change to HS (both $P < 0.001$). During HS but not LS, GFR and filtration fraction (FF) positively correlated with BMI ($R = 0.32$ and $R = 0.28$, respectively, both $P < 0.01$). Consequently, BMI correlated with the sodium-induced changes in GFR ($R = 0.30$; $P < 0.01$) and FF ($R = 0.23$; $P < 0.05$). The effects of HS on GFR and FF were significantly different for BMI ≥ 25 versus < 25 kg/m², namely 7.8 ± 12.3 versus 16.1 ± 13.1 ml/min ($P < 0.05$) and -0.1 ± 2.2 and $1.1 \pm 2.3\%$ ($P < 0.05$). FF was significantly higher in BMI ≥ 25 versus < 25 kg/m², (22.6 ± 2.9 versus $24.6 \pm 2.4\%$, $P < 0.05$) only during HS. ERPF was not related to BMI. Urinary albumin excretion was increased by HS from 6.0 (5.4–6.7) to 7.6 (6.9–8.9). Results were essentially similar after excluding the only two subjects with BMI > 30 kg/m². BMI is a determinant of the renal hemodynamic response to HS in healthy men, and of GFR and FF during HS, but not during LS. Consequently, HS elicited a hyperfiltration pattern in subjects with a BMI ≥ 25 kg/m² that was absent during LS. Future studies should elucidate whether LS or diuretics can ameliorate the long-term renal risks of weight excess.

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Correspondence: GJ Navis, Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. E-mail: G.J.Navis@int.umcg.nl

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Excess body weight is a risk factor for loss of kidney function in different renal disorders.^{1–3} Recent studies showed that a body mass index (BMI) above 25 kg/m² in young adults is associated with an increased risk for end-stage renal disease on long-term follow-up, not only in subjects with a specific renal parenchymal disorder, hypertension, or diabetes, but also without those conditions.^{4–8} The mechanisms underlying the predisposition to renal damage associated with a higher BMI are incompletely understood. In overt obesity, the mechanisms are assumed to involve hypertension,⁹ insulin resistance,¹⁰ as well as an unfavorable hemodynamic profile with renal hyperperfusion and hyperfiltration.^{9,11–13} As a higher BMI is associated with a renal hyperfiltration profile also in healthy subjects without overt obesity, renal hemodynamics could be relevant in the renal effects of an extent of weight excess that does not amount to overt obesity yet.¹²

In population studies, a high BMI was strongly associated with a higher urinary albumin excretion (UAE).^{14,15} Interestingly, an interaction was observed between high dietary sodium intake (estimated by urinary sodium excretion) and excess body weight as risk factors for UAE.¹⁵ The renal mechanisms underlying this interaction would be of interest. Studies in essential hypertensive subjects have shown that a high sodium (HS) intake can elicit albuminuria,¹⁶ with an unfavorable renal hemodynamic profile.¹⁷ This raises the hypothesis that renal hemodynamic factors are involved in the interaction between sodium intake and BMI on UAE. Whereas the renal response to HS has been addressed in various populations,^{12,14,15,17–21} the effect of BMI on the renal hemodynamic response to a HS intake has not been established so far.

Therefore, in the present study we investigated the influence of BMI on the renal hemodynamic response to a shift in sodium intake in healthy young male adults. They were studied during a period of low sodium (LS) (50 mmol/day) and an HS (200 mmol/day) intake, that is, a sodium intake reflecting the lower and upper boundaries of a normal intake.

RESULTS

Median age was 23 years (95% confidence interval: 22–24) and mean BMI 23.0 ± 2.5 kg/m². The distribution of BMI values in our population is shown in Figure 1. The

distribution of BMI was somewhat skewed, with overt obesity (BMI ≥ 30 kg/m²) in two subjects and overweight (BMI ≥ 25 kg/m²) in 16 out of 95 subjects.

Subject characteristics on LS versus HS diet are given in Table 1. It shows that the differences in diet resulted in the expected differences in sodium excretion (U_{Na24}). HS intake caused a significant increase in body weight, consistent with a positive volume balance. Potassium excretion (U_{K24}) was similar during both diet periods. Blood pressure was slightly higher during HS (P = 0.06). In the study group as a whole, there were significant increases in effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) in response to a change from LS to an HS diet, without a change in filtration fraction (FF). Fasting plasma glucose and insulin levels were in the non-diabetic range on both diets, with no differences between LS and HS intake. The UAE was below the threshold

for detection in 23 and 34 out of 95 subjects on LS and HS intake, respectively. As a consequence, paired comparison of UAE between the diets was possible in only 53 subjects. In these subjects, UAE was significantly higher on HS intake. Active plasma renin concentration and aldosterone levels were significantly higher during the LS diet.

On univariate analysis, BMI was significantly associated with GFR and FF (Figure 2, middle panels) during HS intake but not during LS (Figure 2, upper panels). As a consequence, BMI was positively and significantly correlated with sodium-induced changes in GFR and FF (Figure 2, lower panels).

The impact of a BMI ≥ 25 kg/m² on the renal hemodynamic response to HS is shown in Table 2, providing mean values of blood pressure and renal hemodynamics by a break-up by a BMI < or ≥ 25 kg/m². First, it shows that mean arterial pressure and ERPF, and their sodium-induced changes were not affected by BMI on either sodium intake. Second, during LS intake GFR was similar for both groups as well. However, the change in GFR (ΔGFR) elicited by the rise

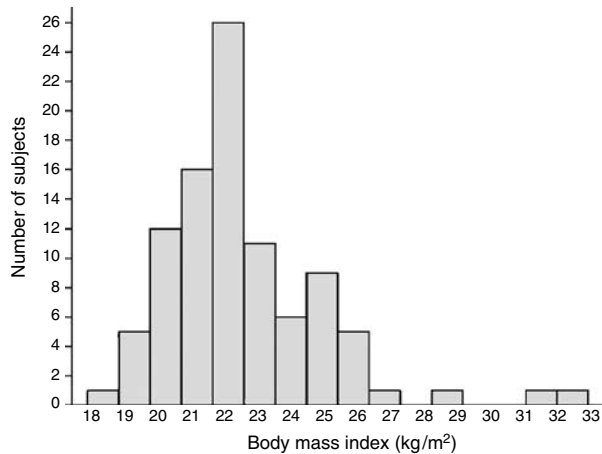


Figure 1 | Distribution of BMI.

Table 1 | Urinary electrolytes, body weight, blood pressure, renal hemodynamics, and metabolic parameters during LS versus HS intake

	Sodium intake		P-value for difference
	50 mmol/24 h	200 mmol/24 h	
U _{Na24} (mmol/24 h)	39 ± 27	251 ± 77	< 0.001
Body weight (kg)	78.7 ± 10.3	80.0 ± 10.3	< 0.001
U _{K24} (mmol/24 h)	83 ± 32	82 ± 28	NS
MAP (mm Hg)	87 ± 7	88 ± 7	0.06
ERPF (ml/min)	563 ± 101	602 ± 115	< 0.001
GFR (ml/min)	127 ± 18	136 ± 20	< 0.001
FF (%)	22.8 ± 3.0	23.0 ± 2.9	NS
Glucose (mmol/l)	4.7 ± 0.7	4.6 ± 0.6	NS
Insulin (mE/l)	8.9 (8.2–10.0)	9.0 (7.6–10.0)	NS
UAE (mg/24 h)*	6.0 (5.4–6.7)	7.6 (6.9–8.9)	< 0.001
APRC (ng ang-I/ml/h)	5.8 (5.2–7.1)	2.2 (1.8–2.6)	< 0.001
Aldosterone (ng/l)	130 (112–138)	40 (32–46)	< 0.001

APRC, active plasma renin concentration; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; HS, high sodium; LS, low sodium; MAP, mean arterial pressure; NS, not significant; UAE, urinary albumin excretion; U_{Na24}, 24-h urinary Na⁺ excretion; U_{K24}, 24-h urinary K⁺ excretion. Data are expressed as mean (± s.d.) or median (95% CI for the median).

*LS: n=72, HS: n=61, paired test in 53 subjects.

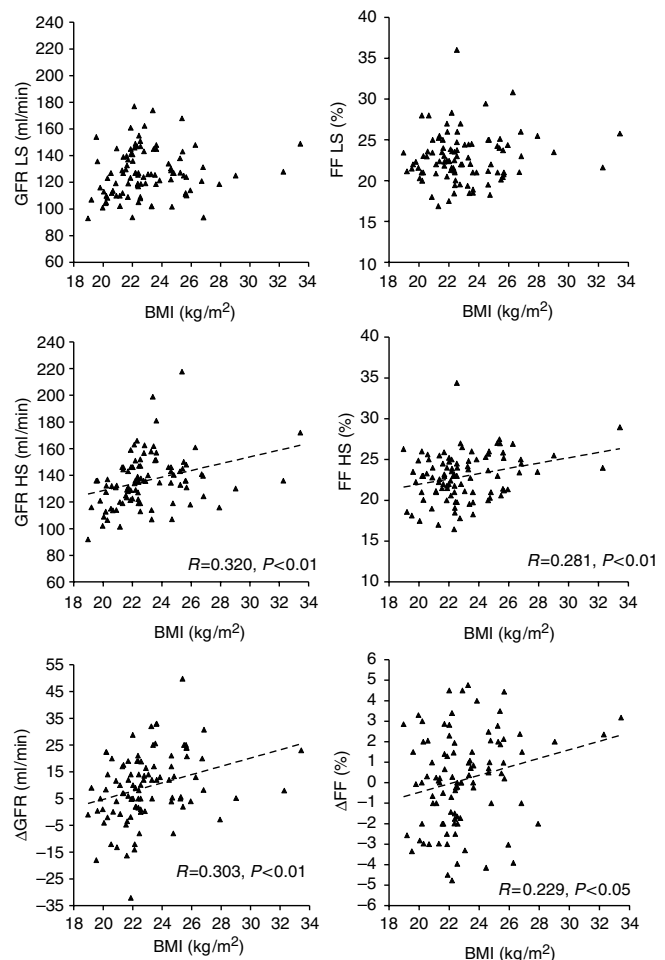


Figure 2 | Scatterplot describing the correlation between BMI and GFR during LS and HS and the sodium-induced change in GFR (ΔGFR): left panels. Correlations between BMI and FF during LS and HS, and sodium-induced change in FF (ΔFF): right panels.

Table 2 | Renal function parameters and urinary electrolytes during LS versus HS intake. Break-up according to BMI ≥ 25.0 kg/m²

	BMI <25 kg/m ² n=77	BMI ≥ 25 kg/m ² n=18	P-value for difference
BMI (kg/m ²)	22.1 \pm 1.4	26.9 \pm 2.4	—
MAP LS (mm Hg)	86 \pm 6	88 \pm 9	NS
MAP HS (mm Hg)	87 \pm 7	91 \pm 7	NS
Δ MAP (mm Hg)	1 \pm 5	2 \pm 6	NS
ERPF LS (ml/min)	568 \pm 106	545 \pm 71	NS
ERPF HS (ml/min)	606 \pm 122	584 \pm 76	NS
Δ ERPF (ml/min)	38 \pm 64	39 \pm 56	NS
GFR LS (ml/min)	127 \pm 18	127 \pm 17	NS
GFR HS (ml/min)	134 \pm 19	143 \pm 23	0.09
Δ GFR (ml/min)	7.8 \pm 12.3	16.1 \pm 13.1	<0.05
FF LS (%)	22.6 \pm 3.0	23.5 \pm 2.7	NS
FF HS (%)	22.6 \pm 2.9	24.6 \pm 2.4	<0.05
Δ FF (%)	-0.1 \pm 2.2	1.1 \pm 2.3	<0.05
U _{Na24} LS (mmol/24 h)	40 \pm 28	34 \pm 18	NS
U _{Na24} HS (mmol/24 h)	250 \pm 78	255 \pm 75	NS
Δ U _{Na24} HS (mmol/24 h)	210 \pm 82	222 \pm 86	NS

BMI, body mass index; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; HS, high sodium diet (200 mmol/24-h); LS, low sodium diet (50 mmol/24-h); MAP, mean arterial pressure; NS, not significant ($P > 0.05$); U_{Na24}, 24-h urinary Na⁺ excretion.

Data are expressed as mean \pm s.d.

in sodium intake was significantly larger in group with BMI ≥ 25 kg/m² ($P < 0.05$). FF was not different during LS intake either, but the response of FF to the change in sodium intake was significantly different between subjects with a BMI <25 and those with a BMI ≥ 25 kg/m², that is, -0.1 ± 2.2 versus 1.1 ± 2.3 , respectively ($P < 0.05$). As a consequence, during HS intake FF was significantly higher in subjects with a BMI ≥ 25 kg/m² than in those with a lower BMI ($P < 0.05$). For GFR, the difference between subjects with BMI ≥ 25 versus <25 kg/m² during HS did not quite reach statistical significance. No impact of BMI was found on glucose, insulin, active plasma renin concentration, and aldosterone and their sodium-induced changes (data not shown).

As described in our Materials and Methods section, the analysis was also performed for renal hemodynamics indexed for height, with results similar to the non-indexed data. Briefly, the differences in GFR on HS intake were also present for GFR expressed per meter of height, being 72 ± 9 and 77 ± 11 ml/min/m for BMI below and above 25 kg/m², respectively ($P = 0.06$). Obviously, the analysis on BMI-related effects on the sodium-induced changes in GFR and FF remained the same. Finally, we repeated our analyses after exclusion of the two subjects with overt obesity: this did not essentially alter the results.

DISCUSSION

This study demonstrates that the renal hemodynamic response to a shift in sodium intake is correlated to BMI in healthy young men, with larger increases in GFR and FF in subjects with a higher BMI. As a consequence, a relationship between higher BMI and higher GFR and FF was present only during high, but not during LS intake. When analyzed by a

break-up by BMI ≥ 25 kg/m², the renal hemodynamic response to HS was significantly larger in subjects with BMI ≥ 25 kg/m², and consequently, a hyperfiltration pattern was observed in these subjects during HS intake only. These results were unaltered after exclusion of the only two subjects with overt obesity, and thus appear to pertain to the overweight range.

The impact of higher BMI as a risk factor for renal damage is increasingly recognized. Earlier studies reported deleterious long-term renal effect of overt obesity in diverse renal conditions.¹⁻³ More recent large epidemiological studies confirmed the increased risk for long-term renal damage in overt obesity, that is, a BMI over 30 kg/m², and moreover demonstrated that less severe weight excess, that is, a BMI ≥ 25 kg/m² was associated with a significantly increased long-term risk for end-stage renal disease as well.^{8,9} This risk was apparent for subjects with renal parenchymal disease, hypertension, or diabetes, but also in the absence of these conditions.

These data prompt for elucidating the underlying mechanisms that predispose to long-term renal damage in subjects with a higher BMI. Studies in overt obesity support a role for renal hemodynamic factors, with hyperfiltration in morbidly obese and obese subjects. These are usually associated with hypertension and impaired glucose tolerance^{9,10,12} but have also been observed independently of these factors.¹⁴ Moreover, BMI-associated hyperfiltration has been reported in the absence of overt obesity, diabetes, or hypertension.¹¹ Together, these data point toward an independent effect of BMI in the overweight range on renal hemodynamics.

Our current study is in line with these prior data. It provides additional insights by demonstrating that a shift in sodium intake modifies the association between BMI and renal hemodynamics by eliciting the BMI-associated hyperfiltration pattern during HS, and ameliorating it during sodium restriction in the same subjects. If indeed renal hemodynamic factors contribute to the long-term risk conferred by a higher BMI, our data might implicate that sodium restriction could exert a beneficial effect on long-term renal risk, but obviously long-term studies would be required to substantiate such an assumption. At any rate, we took care to study a range of sodium intake that bears clinical relevance, as neither the HS intake, nor the LS intake was extreme.

What could be the mechanisms underlying the effect of BMI on the renal response to HS? First, it should be noted that our study was not designed to address mechanisms, as we performed no intervention in candidate pathways. The effect of HS on renal hemodynamics in our subjects with a higher BMI showed a remarkable parallel to studies by ourselves and others in sodium-sensitive hypertensives, demonstrating a change toward hyperfiltration elicited by HS.^{17,19,22,23} Inappropriate activity of the renin-angiotensin system (RAS) during HS was shown to be involved in this unfavorable renal hemodynamic profile.²⁴ In obesity, several

lines of evidence support inappropriate intrarenal RAS activity as well. In an animal model, Barton *et al.*²⁵ found increased intrarenal angiotensin-converting enzyme associated with obesity, mediated by endothelin. In human, interestingly, in follow-up on an earlier observation on the renal response to RAS blockade and BMI in type II diabetes,²⁶ recently a strong correlation was reported between a higher BMI and a larger renal vasodilator response to angiotensin-converting enzyme of angiotensin receptor blocker in healthy subjects on an HS intake.²⁷ The association was best described by a quadratic fit, with a steeper relationship between vasodilator response to RAS blockade and BMI in the obese and morbidly obese range. However, also in subjects with a BMI 25–30 kg/m², a renal vasodilator response to RAS blockade was apparent, whereas this was nonsignificant in lean subjects. These data in the overweight range can be considered in line with our present data, suggesting increased angiotensin-dependent control of renal hemodynamics in overweight as compared to lean subjects. Such effects of angiotensin could well be implicated in our findings. If so, our findings suggest that inappropriate RAS activity is apparently relevant to renal hemodynamics during HS, that is, a condition where RAS activity should normally be suppressed, but not during LS, where it is appropriate for the RAS to be activated. In our study, BMI had no effect on circulating parameters of RAS activity, which is in line with the above studies. However, circulating parameters do not adequately reflect intrarenal RAS activity. Whereas inappropriate RAS activity thus may be involved in our findings, other neuro-humoral pathways such as the renal sympathetic nervous system²⁸ and endothelin²⁹ could also be involved.

Several lines of evidence suggest a link between obesity, insulin resistance, and RAS activity. A higher BMI is associated with increasing insulin resistance.^{30,31} Hepatic production of angiotensinogen is enhanced by higher plasma insulin levels.^{32,33} In addition, increased insulin resistance was reported during HS in rats³⁴ and in healthy normotensive males.³⁵ Thus, the combination of overweight and HS could induce inappropriate RAS activation by elevated insulin levels. In contrast to prior reports in healthy subjects³⁶ and in type II diabetes,³⁷ however, in our population no differences in insulin between LS and HS could be demonstrated, which renders this possible mechanism less likely.

For our study, we selected young healthy volunteers, to avoid the effects of subclinical renal target organ damage or of hypertension on the renal response to HS. However, by these selection criteria, our population might well include subjects that will develop hypertension at middle age, be it in association with sodium sensitivity or not, with the corresponding renal hemodynamic risk profile. It would be of interest to see whether the current renal response to sodium predicts hypertension on long-term follow-up, but attempts to identify individuals prone to develop hypertension based on the current data would be too speculative. At any rate, the renal response to HS in the present study was

not associated with the sodium sensitivity of blood pressure in these normotensive individuals.

What are the clinical implications of our findings? The impact of excess sodium intake as a renal risk factor was emphasized recently.^{38,39} Our data are in line with the alleged role of excess sodium as a renal risk factor, and provide a possible mechanism underlying the interaction between BMI and HS on renal risk that was observed in epidemiological studies. Our subjects were young and the observed effects of BMI were apparently not explained by overt obesity. In young adults, overt obesity is still relatively rare, and overweight is much more frequent, as also shown by the distribution of BMI in our population. As a BMI ≥ 25 kg/m² is already associated with an increased long-term risk for end-stage renal disease, on a population basis the long-term renal impact of the interaction between sodium status and BMI can potentially be substantial, but longitudinal data would be needed to support this assumption.

As a possible marker of subclinical renal risk, we measured UAE. As expected, this was normal in all subjects, and in fact it was below the level of detection in many cases, so in only 53 subjects we were able to compare UAE on LS versus HS. These restrictions taken in mind, it is nevertheless remarkable that UAE was higher on HS. This observation has not been made in healthy subjects before, but is in line with prior cross-sectional observations in epidemiological studies¹⁵ and with studies in type II diabetics with microalbuminuria.⁴⁰ We did not detect an interaction between BMI and sodium intake on UAE, but obviously the power of our study to detect such an interaction was insufficient.

A limitation of our study is that that we measured renal hemodynamics after only 1 week of diet. Whereas this time frame is sufficient to restore sodium balance after a change of diet, it is not sure whether renal hemodynamics remain similar during long-term changes in sodium status. For between-individual comparison, renal hemodynamics are usually expressed per 1.73 m² body surface area. However, a rise in BMI elicits a rise in body surface area. Hence, indexing for body surface area will bias analyses that address effects of BMI.^{41,42} Therefore, we present the non-indexed data, but additionally repeated the analyses after indexing for height, with similar results. Moreover, our data on the individual sodium-induced changes in renal hemodynamics are independent of indexing, and thus are robust against assumptions about the appropriate adjustment.

This is the first study to show that BMI is an important determinant of the renal hemodynamic adaptation to an HS intake in young healthy men. Moreover, our data show that HS elicits a hyperfiltration pattern in subjects with a BMI ≥ 25 kg/m², which is absent during LS. These data suggest that renal hemodynamic factors may be involved in the interaction between BMI and sodium intake on the kidney that was observed in prior epidemiological studies, and prompt to explore the role of sodium intake as a modifier of the long-term renal risk associated with weight excess.^{15,38}

MATERIALS AND METHODS

Subjects

The study population consisted of 95 healthy normotensive men not selected for BMI. Normal blood pressure was confirmed by repeated non-invasive automatic blood pressure assessment (Dinamap) and defined as systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg. The study was approved by the local medical ethics committee, in accord with the Declaration of Helsinki Principles, and all participants gave written informed consent. All medical histories were without significant disease, and results of physical examination were unremarkable.

Study protocol

Subjects were studied at the end of two different 7-day periods, during which they used a LS diet (50 mmol Na⁺/day) and an HS diet (200 mmol Na⁺/day), respectively. Potassium intake was standardized at 80 mmol/day. Otherwise, the subjects continued their usual food habits. For assessment of dietary compliance and sodium balance, 24 h urine was collected at day 4 and day 6 during each period. During both periods, the subjects were ambulant and continued their normal activities.

At day 7 of both study periods, the subjects reported at the research unit at 0800 hours, after having abstained from food and alcohol overnight. Height and body weight were measured at the start of this day and BMI was calculated as the ratio of body weight (kg) and the square of height (m).

During the study day, subjects remained in a semi-supine position except during voiding. One intravenous cannula was inserted in each forearm. One was used for infusion of tracers and the other for infusion of fluids and blood sample withdrawal. Blood was collected for fasting glucose and insulin determination. At 1100 hours, blood was withdrawn for determination of active plasma renin concentration and aldosterone. Sodium intake during the day was adjusted according to the actual diet in the concerning diet period. To ensure sufficient urine output, 250 ml of 5% glucose solution was administered in the right antecubital vein and subjects were provided with 250 ml of oral fluids every hour. After a 2 h run-in period, GFR and ERPF were measured as the clearances of constantly infused ¹²⁵I-Iothalamate and ¹³¹I-Hippuran, respectively. In this set-up, GFR is measured as the urinary clearance of ¹²⁵I-Iothalamate, and corrected for voiding errors by the ratio of plasma to urinary clearance of ¹³¹I-Hippuran, as described in more detail previously.⁴³ The coefficient of variation of this method is 2.5% for GFR and 5% for ERPF. FF was calculated as the ratio of GFR and ERPF and expressed as percentage (%). Blood pressure was assessed with an automatic device (Dinamap) at 15 min intervals. Mean arterial pressure was calculated as diastolic pressure plus one-third of the pulse pressure.

Chemical analysis of urine and blood samples

Urinary concentrations of sodium and potassium were measured by standard auto-analyser technique (MEGA, Merck, Darmstadt, Germany). UAE was determined by nephelometry with a threshold of 2.3 mg/l (Dade Behring Diagnostic, Marburg, Germany). Insulin was determined on an AxSym with a threshold of 1.0 μU/ml and intra-assay and inter-assay coefficients of variation of 2.6 and 4.3%, respectively (Abbott BV, Amstelveen, The Netherlands). Active plasma renin concentration was determined in terms of angiotensin I generation using a radioimmunoassay.⁴⁴ Aldosterone was measured with a commercially available radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, CA, USA). Plasma

glucose was determined by glucose-oxidase method (YSI 2300 Stat plus, Yellow Springs, OH, USA).

Data analysis

Data were analyzed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA). Data with a normal distribution are expressed as mean ± s.d. Non-parametric data are given as median (95% confidence interval). Simple Pearson's parametric correlation was used for continuous analysis of the influence of BMI on renal hemodynamics. The average BMI over both conditions of sodium intake was used for analysis. For the total group, the effect of the change in sodium intake was assessed by a paired sample *t*-test for parametric data and a Wilcoxon's signed rank test for non-parametric data. Furthermore, data were analyzed according to the break-up by BMI ≥ 25 kg/m², that is, the usual cutoff for overweight, using a Student's *t*-test to compare the groups with BMI ≥ 25 and < 25 kg/m².

Data on renal hemodynamics were analyzed both as crude values and after normalization for height. We refrained from normalization by body surface area as such normalization by definition will confound analyses for BMI-related effects, and for this reason, normalization by height has been recommended.^{41,45} In this paper, we present the analysis as carried out on crude data, but additionally we performed the same analyses after indexing for height, with similar outcomes. A two-sided *P*-value < 0.05 was considered to be significant.

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