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Short-term moderate sodium restriction induces relative hyperfiltration in normotensive normoalbuminuric Type I diabetes mellitus

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Abstract

Aims/hypothesis. Type I (insulin-dependent) diabetes mellitus is associated with an increased extracellular volume. Sodium restriction might seem a logical form of treatment but data on its renal effects is conflicting. We therefore studied the effects of sodium restriction on renal haemodynamics in uncomplicated Type I diabetes mellitus.
Methods. Uncomplicated Type I diabetic patients ($n = 24$) and matched control subjects ($n = 24$) were studied twice in random order: after a week of 50 mmol or after 200 mmol sodium intake, respectively. The diabetic patients were studied under normoglycaemic clamp conditions. Glomerular filtration rate and effective renal plasma flow were measured as the clearances of iothalamate and hippuran, respectively.
Results. During liberal sodium intake, glomerular filtration, effective renal plasma flow and filtration fraction were similar between the diabetic patients and the control subjects. Sodium restriction decreased the effective renal plasma flow in both groups, whereas glomerular filtration rate only decreased in the control subjects. Consequently, in the diabetic patients, the filtration fraction was increased on low sodium ($4.1 \pm 8.4\,\%$, $p < 0.05$ vs liberal sodium). As a consequence, filtration fraction (24.0 ± 2.6 vs $22.1 \pm 2.0\,\%$, $p < 0.05$) and glomerular filtration (119 ± 14 vs 110 ± 13 ml/min, $p < 0.05$) were higher in the diabetic patients than in the control subjects during sodium restriction.
Conclusion/interpretation. Short-term moderate sodium restriction induces relative hyperfiltration in uncomplicated Type I diabetes. This could indicate an increased intraglomerular pressure. Sodium restriction could be an unfavourable preventive approach in diabetes mellitus but its long-term effects are not known. [Diabetologia (2002) 45:535–541]

Keywords Type I diabetes mellitus, sodium intake, renal haemodynamics, renin-angiotensin system, diabetic nephropathy.

Diabetic nephropathy is one of the most serious complications of diabetes mellitus. Nephropathy develops in approximately 35 % of diabetic patients [1]. Preventive measures include good metabolic control and rigorous antihypertensive treatment, preferably by renin-angiotensin system (RAS) blocking agents [2]. Early abnormalities preceding overt nephropathy include microalbuminuria, a rise in blood pressure and an increase in intraglomerular pressure [3, 4]. Volume expansion is probably relevant in these processes because renal sodium excretion is known to be blunted in diabetic patients [5, 6, 7, 8, 9], an effect that might be mediated by the sodium retaining effects of insulin [10, 11].

Considering the abnormalities in extracellular volume, dietary sodium restriction would seem a logical form of treatment. However, low sodium intake acti-

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Abbreviations: MAP, Mean arterial pressure; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; FF, filtration fraction; RVR, renal vascular resistance; RAS, renin-angiotensin system; PRA, plasma renin activity

vates the RAS [10, 11] and an increase in RAS-activity has been proposed to play a role in the development of diabetic nephropathy, as suggested by the preventive effect of ACE-inhibitors on the development of diabetic nephropathy [2, 12]. Thus, sodium restriction could theoretically exert unfavourable effects in the diabetic kidney.

Reports about the renal effects of sodium restriction in diabetes mellitus are scarce and data are conflicting. In the streptozotocin rat model, both the augmented renal plasma flow (RPF) and glomerular hyperfiltration were improved by sodium restriction [13, 14, 15]. In contrast, an increase in RPF and glomerular filtration rate (GFR) with sodium restriction has been reported [16]. In humans, two small studies are available so far, using a rigorous restriction in dietary sodium (i.e. to 20 mmol/day), yielding conflicting results [17, 18].

To investigate the renal effects of a dietary sodium restriction that is feasible in clinical practice we evaluated the renal haemodynamic effects of 50 mmol compared with a 200 mmol sodium intake in uncomplicated Type I diabetic patients on exogenous insulin and healthy control subjects.

Subjects and methods

Subjects and study design. Twenty-four normotensive (systolic pressure < 140 mmHg, diastolic pressure < 85 mmHg), normoalbuminuric (< 30 mg/24hr) Type I diabetic patients were compared with 24 healthy control subjects according to a parallel open-label randomized cross-over design. Participants were matched for age (within 3 years), sex (M/F), and body mass index (< 3 kg/m^2, BMI was calculated as weight divided by height squared and expressed in kg/m^2). All diabetic patients suffered from ketosis-prone diabetes mellitus and their age of onset was less than 35 years. Metabolic control was adequate in diabetic patients, as indicated by an HbA_{1c} concentration of less than 8.0 % in all. The diabetic patients received an average of 61 ± 18 units of insulin during the days before the study was carried out, using modern insulin schemes consisting of long-acting insulin before the night and three injections of short-acting insulin before the meals. The study was approved by the local medical ethics committee and all participants gave their written informed consent.

The participants were studied twice, and counselled by a research dietician who advised a low sodium diet (50 mmol of sodium a day) and a liberal sodium diet (200 mmol of sodium a day). The sequence of the diets was randomized by drawing an allocation number from closed envelopes. The diet periods were separated by at least one week (10 to 17 days) to rule out carry-over effects. Both diets were normocaloric and were started 7 days before each day of investigation. During the diet periods the subjects were ambulant and continued their normal daily activities. The low and liberal sodium diets were randomised and adherence was checked by measuring sodium excretion in 24 h urine collections on the third or fourth day of the diet, as well as on the day prior to the study day.

Experiments. On each study day the subjects reported to the hospital research unit at 0730 hours after a fast, having refrained from food, alcohol, drinking and strenuous exercise for 12 h. The experiments started at 0800 hours. Two 18-gauge peripheral venous cannulas were inserted into an antecubital vein of the left and right arm for infusion of isotopes, glucose and insulin and for drawing of blood samples. During the experiment, subjects remained in the semisupine position in a quiet room. They had 250 ml of drinks without caffeine each hour. Smoking was not allowed during the study day.

The diabetic patients were studied using the euglycaemic clamp technique, whereby normoglycaemic conditions (blood glucose 5.0 mmol/l) were attained using a low insulin infusion ($30\ mU \cdot kg^{-1} \cdot h^{-1}$) with a variable glucose infusion (dextrose 20 % to which 20 ml/l KCl was added to prevent hypokalaemia).There were no differences in the amount of glucose required to maintain euglycaemia during low and liberal sodium intake. The healthy subjects were not studied using this technique, assuming a normal blood glucose regulation.

After 2 h of equilibration, blood was sampled in pre-chilled tubes hourly, during two consecutive hours. Blood samples were centrifuged at 3000 revolutions per min at 4 °C. Urine was collected after blood samples were taken. Blood pressure was measured using an automated device (Dinamap, Criticon, Tampa, Fla., USA) at 15 min intervals. Hormonal parameters were measured at 1000 hours and at 1200 hours and the average values of both measurements were used for analysis.

Renal function measurements. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by constant infusion of radiolabelled tracers, ^{125}I-iothalamate and ^{131}I-hippurate, respectively [20]. After drawing a blank blood sample, a priming solution containing 0.04 ml/kg body weight of the infusion solution (0.04 MBq of ^{125}I-iothalamate and 0.03 MBq of ^{131}I-hippurate) plus an extra of 0.6 MBq of ^{125}I-iothalamate was given at 0800 hours, followed by infusion at 12 ml/h. In order to attain stable plasma concentrations of both tracers, a 2 h stabilisation period followed, after which baseline measurements started at 1000 hours. The clearances were calculated as (U*V)/P and (I*V)/P, respectively. U*V represents the urinary excretion of the tracer, I*V represents the infusion rate of the tracer; and P represents the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead space, by multiplying the urinary clearance of ^{125}I-iothalamate with the ratio of the plasma and urinary clearance of ^{131}I-hippuran [21]. The filtration fraction (FF) was calculated as the ratio of GFR and effective renal plasma flow (ERPF) and expressed as percentage. Renal vascular resistance (RVR) was calculated as mean arterial blood pressure (MAP) divided by ERPF. Glomerular filtration rate and ERPF were corrected for $1.73 m^2$ of body surface area. This method has a day-to-day variation coefficient of 2.5 % for GFR and 5 % for ERPF [21].

Laboratory methods. Serum electrolytes, creatinine, liver enzymes and blood count were measured by an automated multi-analyser (MEGA, Merck, Darmstadt, Germany). Plasma glucose concentrations were measured using the APEC glucose analyser (APEC, Danvers, Mass., USA). Plasma renin activity (PRA) was measured using an in-home radioimmunoassay. HbA_{1c} was measured by high-performance liquid chromatography (Bio-Rad, Veenendaal, The Netherlands; normal range 4.6–6.1 %).

Statistical analysis. A power-analysis was done, based on GFR as well as filtration fraction (FF) (i.e., both parameters for hyperfiltration) as primary end-points. For both GFR and FF the SD of the population is approximately 10 %. Thus, our study was powered to detect a 10 % difference in GFR and FF between the groups, with an α of 0.05 and a β of 0.90 with

Table 1. Clinical and laboratory characteristics during liberal (lib S, 200 mmol sodium per day) and low (low S, 50 mmol sodium per day) sodium intake in Type I diabetic patients and healthy control subjects

	Type I diabetic patients[a]	Control subjects[a]	*p* value
n (M:F)	24 (15:9)	24 (15:9)	NS
Age (yr.)	28.2 ± 6	25.1 ± 4	NS
Body mass index Lib S (kg/m^2)	23.7 ± 2.2	22.2 ± 3.3	NS
Body mass index Low S (kg/m^2)	23.5 ± 2.2	21.8 ± 3.3	NS
HbA_{1c} (%) Lib S	7.4 ± 0.6	5.2 ± 0.1	< 0.001
HbA_{1c} (%) Low S	7.4 ± 0.5	5.2 ± 0.2	< 0.001
UNaV (mmol/24 h) Lib S	249 ± 70.7	254 ± 58.4	NS
UNaV (mmol/24 h) Low S	38 ± 13.1*	45 ± 28.2*	NS
UalbV(mg/24 h) Lib S	7.2 ± 3.0	7.5 ± 3.5	NS
UalbV(mg/24 h) Low S	8.6 ± 9.0	7.2 ± 3.0	NS
PRA (nmol AngI/l/h) Lib S	0.19 ± 0.1	0.21 ± 0.2	NS
PRA (nmol AngI/l/h) Low S	0.70 ± 0.4*	0.65 ± 0.5*	NS

[a] The mean ± SD is given
* $p < 0.001$ vs Lib S
UNaV urinary sodium excretion, *UalbV* urinary albumin excretion

Table 2. Blood pressure and renal haemodynamics during liberal (Lib S) and low (Low S) sodium intake in Type I diabetic patients (DM) and control subjects (C)

	DM *Lib S*[a]	DM *Low S*[a]	C *Lib S*[a]	C *Low S*[a]
MAP (mmHg)	90 ± 8	87 ± 7	89 ± 7	88 ± 7
GFR (ml · min^{-1} · 1.73m^{-2})	123 ± 10	119 ± 14***	120 ± 18	110 ± 13**
ERPF (ml · min^{-1} · 1.73m^{-2})	538 ± 77	498 ± 59**	539 ± 68	502 ± 58**
FF (%)	23.1 ± 2.6	24.0 ± 2.6*, ***	22.5 ± 2.9	22.1 ± 2.0
RVR (mmHg/l min)	154 ± 3	178 ± 3**	151 ± 2	177 ± 3**

[a] Data in means ± SD
* $p = 0.05$ compared with liberal sodium
** $p = 0.001$ compared with liberal sodium
*** $p = 0.05$ compared with control subjects

22 subjects for each group. In both groups, 24 subjects were included to allow for possible drop-outs. Secondary end-points were blood pressure and renal plasma flow (ERPF). Data are expressed as means ± SD and 95% confidence intervals. Unpaired Student's *t* tests were used to test inter-group differences. Paired variables *t* tests were used to compare data during the low and liberal sodium situation in each subject. A two sided *p*-value of less than 0.05 was considered to be significant. Bivariate correlation analysis was carried out for a possible relation between daily insulin dose and the response to sodium restriction.

Results

Patient characteristics (Table 1). The average duration of diabetes was 12.3 ± 5.5 years, with a mean age of onset of 15.8 ± 6.5 years. During liberal sodium intake, BMI was 23.7 ± 2.2 kg/m^2 in diabetic patients and 22.2 ± 3.3 kg/m^2 in control subjects (NS). During low sodium diet both groups showed a non-significant decrease in BMI (diabetic group 23.5 ± 2.2 kg/m^2, control group 21.8 ± 3.3 kg/m^2, NS). Mean HbA_{1c} concentration was 7.4 ± 0.5% in the diabetic group, reflecting good metabolic control. Compliance to the low as well as to the liberal sodium diet was defined by a sodium excretion of < 60 mmol/l/24 h for low and > 180 mmol/24 h for the liberal sodium diet. The values for UNaV show that compliance was satisfactory in both groups. During liberal sodium intake, PRA was similar in both groups. During low sodium, PRA increased similarly in each group.

Systemic and renal haemodynamic effects of sodium restriction. Mean arterial blood pressure was similar in both groups during liberal sodium intake. The decreases in MAP during low sodium diet were not significant in either group (Table 2).

During liberal sodium, ERPF and GFR were similar between the diabetic patients and the control subjects. Accordingly, FF was similar as well. Sodium restriction induced a similar decrease in ERPF in both groups (–6.8 ± 8.7% in the diabetic group, –6.5 ± 6.9% in the control group, $p < 0.001$ vs liberal sodium for both groups, Table 2, Fig. 1). Furthermore, sodium restriction induced a decrease in GFR in the control subjects (–7.6 ± 9.3%, $p < 0.001$ vs liberal sodium, Fig. 1). In the diabetic patients however, sodium restriction did not result in a consistent reduction of GFR (Fig. 1). As a result, during low sodium GFR was higher in the diabetic patients than in the control subjects ($p < 0.05$, Table 2).

Consequent to the responses of MAP and ERPF, renal vascular resistance (RVR) increased similarly during low sodium diet in the diabetic and control groups (by 18.0 ± 16.8% and 17.8 ± 14.4% respec-

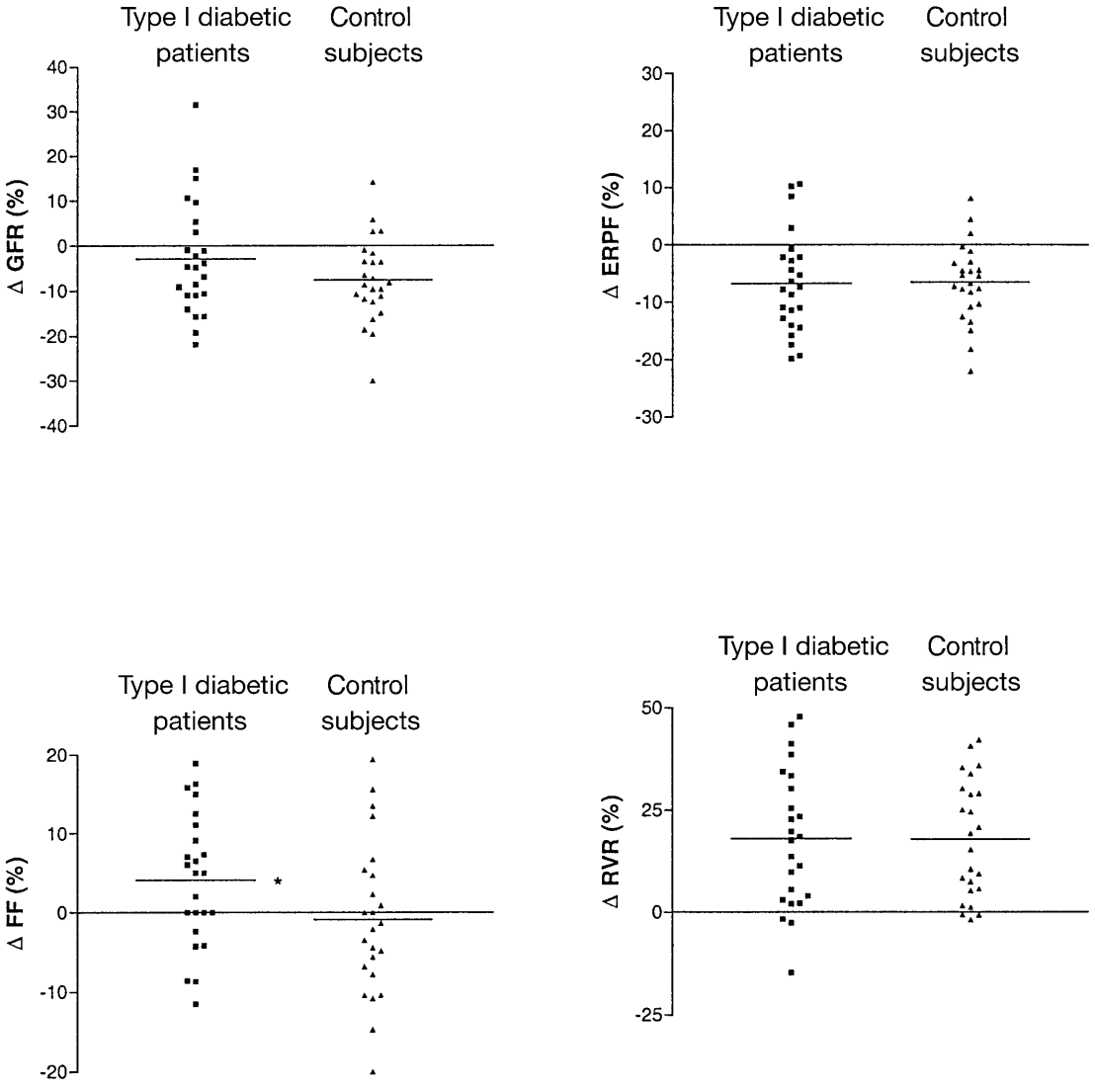

Fig. 1. Per cent changes of GFR, ERPF, FF and RVR induced by low sodium intake for diabetic patients and control subjects. Mean values are indicated by the horizontal lines. * = $p < 0.05$ diabetic patients vs control subjects

tively, $p < 0.001$ vs liberal sodium, Table 2, Fig. 1). In the control subjects, the decreases in ERPF and GFR during sodium restriction were proportional, as indicated by the virtually unchanged filtration fraction (Table 2, Fig. 1). In the diabetic group however, FF was increased by low sodium (increase 4.1 ± 8.4 %, $p < 0.05$ vs liberal sodium). As a consequence, during low sodium, FF was higher in the diabetic patients than in the control subjects ($p < 0.05$, Table 2).

No associations between daily insulin dose and the responses to sodium restriction could be detected: the correlation coefficients between insulin dose and changes in GFR and FF were 0.1 and 0.2 (both NS), respectively.

Discussion

Our study shows that a short-term moderate sodium restriction induces relative hyperfiltration in normotensive, normoalbuminuric Type I diabetic patients.

The diabetic subjects were tested using euglycaemic clamp, with low dose insulin infusion. Insulin is known to stimulate sodium retention, vasodilation and sympathetic activity [21, 22, 23, 24, 25], which could have influenced our results. Refraining from the euglycaemic clamp would have most likely exerted more bias in renal function. It is known that hyperglycaemia affects renal haemodynamics, resulting most likely from RAS-activation [26, 27, 28, 29]. The low dose of insulin that we used provides stable peripheral insulin concentrations of approximately 30 mU/l [30], i.e. slightly below the average insulin concentrations during daily life in diabetic patients. Therefore, our experimental conditions during the renal function studies more or less mimic those in a reasonably well-regulated diabetic patient during daily life. The healthy control subjects did not receive

insulin infusion, as insulin could exert effects on renal haemodynamics [31]. Thus, as inevitable in studies comparing diabetic patients and control subjects, study conditions did not completely match in both groups.

We found that low sodium diet induced a similar decrease in ERPF, with a corresponding increase in overall RVR in diabetic patients and control subjects, whereas the effect on FF was different. This suggests that sodium restriction differentially affected the balance between afferent and efferent vascular tone in diabetic patients compared to control subjects, with a lower contribution of afferent tone in total RVR in diabetes during low sodium. In the human studies to date, obviously intrarenal haemodynamics could not be measured directly. The higher GFR with unaltered ERPF is, however, highly suggestive of alterations in afferent and efferent balance. There are two possible explanations for this phenomenon.

First, there could be an impaired afferent glomerular vasoconstrictor function in diabetes mellitus [32, 33]. These afferent abnormalities have been attributed to alterations in tubuloglomerular feedback in the diabetic state. Proximal tubular reabsorption of sodium is increased in experimental as well as in human Type I diabetes, as shown by lithium clearance studies [34, 35, 36]. These studies as well as recent animal data have shown that by this increased proximal reabsorption, distal tubular delivery of sodium decreases, thereby deactivating the tubuloglomerular feedback signal, resulting in afferent vasodilatation [35, 37]. By this mechanism dietary sodium restriction could paradoxically aggravate glomerular hyperfiltration in uncomplicated diabetes mellitus [37].

Second, exaggerated activation of the RAS should be considered. However, we found no differences in circulating PRA, as both groups showed a similar rise in PRA during sodium restriction. Increasing evidence suggests the existence of an intrarenal RAS, that acts independently from the systemic RAS [38, 39]. A study in patients with Type II (non-insulin-dependent) diabetes mellitus with nephropathy showed an enhanced renal vasodilator response to the administration of ACE inhibitors as well as to AngII antagonists even when PRA was low, suggesting intrarenal RAS-activation in diabetic nephropathy [40, 41]. Furthermore, hyperglycaemia has been associated with intrarenal RAS activation in healthy humans. Captopril enhances the renal vasodilatation induced by hyperglycaemia without alteration of circulating PRA, suggesting intrarenal RAS-activation by hyperglycaemia [28]. Because the RAS has a predominant efferent vasoconstrictor effect [42], a more pronounced activation of the intrarenal RAS in the diabetic patients in the current study could be an explanation for the observed difference in the balance between afferent and efferent vascular tone.

Thus, failure of adequate afferent glomerular autoregulation, and/or excessive efferent glomerular arteriolar vasoconstriction due to an overproduction of AngII could explain the relation between lowering sodium intake and the increased filtration fraction. As the latter could be the reflection of increased intraglomerular pressure, sodium restriction as such could induce an unfavourable renal haemodynamic response in diabetes.

In experimental diabetes, studies on the renal effects of sodium restriction yielded conflicting results. One group reported that diabetic hyperfiltration was corrected by sodium restriction [14], while others found an increase in renal hyperfiltration [16]. The renal effects of sodium restriction in human diabetes were examined in only two previous studies [17, 18]. In nine normoalbuminuric patients, GFR and ERPF were reduced by lowering sodium intake, with no change in FF [18]. Values of ERPF and GFR were higher than ours on both studied conditions, which could be due to a longer duration of diabetes or higher HbA_{1c} concentrations. There were however no healthy control subjects, so a direct comparison with our findings cannot be made.

Restriction of dietary sodium to 20 mmol/day was found to induce a fall in RVR, accompanied by a rise in ERPF as well as GFR, in spite of an appropriate rise in PRA in Type I diabetic patients. In the control group, ERPF and GFR were unaltered [17]. Thus, in accord with our data, diabetic patients in that study responded differently to low sodium than the control subjects, with relative hyperfiltration during low sodium. In contrast to our findings, the hyperfiltration during low sodium was due to hyperperfusion; i.e. a rise in renal blood flow with a fall in RVR. It might be that the less rigorous metabolic control (limit for inclusion was a $HbA_{1c} < 10\,\%$, vs 8.5 % in our study), and the concomitant hyperfiltration already present during liberal sodium resulted in a greater propensity to renal vasodilation [28, 43]. However, differences in experimental set-up could account for the differences in the effects of low sodium on renal perfusion, as suggested by the differences in effect of low sodium on RVR in the healthy control subjects as well. In our control subjects RVR was increased by low sodium as in earlier findings [19, 44]. This renal vasoconstrictive response was shown to be mediated by the RAS [19, 44]. Such a renal vasoconstrictive response was absent in the control subjects in [17]. The reason for the discrepancy is not clear but perhaps the less pronounced waterloading in our protocol allows for more accurate detection of RAS-mediated renal responses [45].

Our data suggest that sodium restriction might not be suitable for prevention of nephropathy. Our data, however, were obtained after only one week of sodium restriction and thus require confirmation after long-term sodium restriction. In addition, early hy-

perfiltration as described in the literature usually occurs during liberal sodium, in a non-normoglycaemic condition. The interaction between glycaemia and sodium restriction is thus not clear. Moreover, the inter-individual differences in the renal response to sodium restriction in the diabetic patients indicate that individual factors should be considered in recommendations for an optimal sodium intake. Finally, hyperfiltration often predicts nephropathy but not inevitably so [4, 46, 47, 48], thus the pathogenetic relevance of our findings for the likelihood of later nephropathy remains to be investigated. In this respect it would be of interest to investigate the renal response to sodium restriction in patients with microalbuminuria. Our data do not implicate that sodium restriction should be discarded in diabetic patients. RAS-blockade by ACE inhibition or AII antagonists is one of the main measures to prevent diabetic nephropathy. In non-diabetic subjects sodium restriction enhances the renoprotective effects of RAS-blockade [49, 50]. Thus, it would be worthwhile to investigate the effects of sodium restriction combined with RAS-blockade in diabetic patients as well.

In summary, short-term moderate sodium restriction induces relative hyperfiltration (but not hyperperfusion) in uncomplicated, normoalbuminuric Type I diabetic patients. The findings are compatible with an altered balance between the afferent and efferent vascular tone associated with increased intraglomerular pressure, elicited by sodium restriction. The intrarenal mechanisms of this response to low sodium, however, needs to be investigated further. Moderate sodium restriction as such could be unsuitable as a preventive approach in diabetes but long-term studies and studies in albuminuric patients are needed to substantiate this assumption.

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