Proximal glomerulo-tubular balance in patients with Type 1 (insulin-dependent) diabetes mellitus

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Summary. To evaluate the glomerulo-tubular balance of sodium and water in the proximal tubules of diabetic patients with elevated glomerular filtration rate, the renal plasma clearance of lithium and the glomerular filtration rate (⁵¹Cr-EDTA plasma clearance) were determined simultaneously in 11 ambulatory Type 1 (insulin-dependent) diabetic patients (aged 25–35 years) with no evidence of diabetic nephropathy and in 10 age-matched healthy subjects. The renal plasma clearance of lithium, which is a measure of flow from the proximal tubule into the thin descending limb of the loop of Henle, did not differ between diabetic and control subjects (28.9 ± 4.0 versus 28.3 ± 5.1 ml/min per 1.73 m^2 surface area, mean $\pm$ SD), whereas the glomerular filtration rate in the diabetic patients was significantly higher than in the control sub-

jects (136 ± 10.2 versus 108 ± 13.6 ml/min per 1.73 m^2 , $p < 0.001$). The same held true for the fractional reabsorption rate in the proximal tubules (78.7 ± 3.2 versus $73.6 \pm 4.9\%$, $p < 0.02$). The results indicate that the elevation of the glomerular filtration rate in diabetic patients is associated with a parallel increase in the proximal reabsorption rate. This type of glomerulo-tubular balance implies that the flow of water and flux of sodium to the segments distal to the proximal tubule are kept constant during variations in the glomerular filtration rate.

Key words: Type 1 diabetes, glomerulo-tubular balance, glomerular filtration rate, lithium clearance.

It is well-established that the glomerular filtration rate (GFR) is increased significantly in Type 1 diabetic patients before the onset of clinical nephropathy [1–5]. Similar results have been reported in insulin-treated streptozotocin/alloxan-diabetic rats [6–8] in which the elevation of whole kidney GFR reflects an increase of GFR in the single nephron.

As known from micropuncture studies in animals, the general feature of the relationship between GFR and reabsorption of sodium and water in the proximal tubule is a proportionality between changes of these measures both under physiological and several pathophysiological conditions [9–13]. This glomerulo-tubular balance implies that the flow of water and flux of sodium into the thin descending limb of the loop of Henle is kept fairly constant over a wide range of GFR-variation [14].

Several reports within the last few years have shown that the renal plasma clearance of lithium is a reliable measure of flow from the straight part of the proximal tubule into the thin descending limb of the loop of Henle [15–17]. From simultaneous determination of GFR and the renal plasma clearance of lithium, it has thus become possible to assess the relationship between

GFR and proximal reabsorption in man. In the present study we have determined this relationship in Type 1 diabetic patients and compared the results with those obtained from a group of age-matched control subjects. The aim of the study was to investigate whether the glomerulo-tubular balance for sodium and water in the proximal tubule is preserved in diabetic patients with elevated GFR.

Subjects and methods

Subjects

Fourteen ambulatory Type 1 diabetic patients (two females, 12 males) and 13 age-matched healthy staff-members (two females, 11 males) gave their informed written consent to the study, which was approved by the local Ethical Research Committee. Due to hypoglycaemia during the investigation and/or incomplete bladder emptying (judged from creatinine clearance determined twice), a total of six subjects were excluded leaving 11 diabetic patients (one female, 10 males) and ten healthy subjects (all men). Clinical data for the 21 individuals are given in Table 1. None of the patients had proteinuria when tested with Albustix and all had a serum creatinine concentration within normal limits. None received any medication besides insulin.

In the evening before the study each participant was given 16.2 mmol of lithium (Li_2CO_3) orally. Until the end of the investiga-

Table 1. Clinical data in 11 diabetic patients and 10 healthy subjects

Subjects	Age (years)	Duration of diabetes (years)	Height (cm)	Body weight (kg)	Body surface area (m ²)	Mean plasma glucose (mmol/l)	Mean urinary glucose (mmol/h)	Insulin requirement (U/24 h)
Diabetic patients								
1	33	0.5	177	67.8	1.84	13.4	9.5	12
2	34	1	182	73.4	1.94	10.1	0.4	24
3 ^a	29	1	172.5	69.5	1.82	11.9	4.0	32
4	33	5	179	83.9	2.03	16.6	10.1	32
5	34	5	169	75.5	1.86	13.1	8.3	40
6	35	8	175.5	66.3	1.81	10.2	16.4	36
7	31	5	182	63.5	1.82	13.9	3.5	44
8	29	4	182	77	1.98	13.8	3.2	52
9	25	24	174	72	1.86	9.9	1.3	52
10	32	17	176	64.5	1.79	10.9	2.2	40
11	31	21	178	82.3	2.00	7.8	0.6	72
Mean ± SD	31.5 ± 2.9	8.3 ± 8.4	177 ± 4.2	72.3 ± 6.9	1.89 ± 0.09	12.0 ± 2.5	5.4 ± 5.0	40 ± 16
Normal subjects								
1	33		180	67.3	1.86	4.7		
2	36		180	81.8	2.02	5.8		
3	31		176	71.5	1.87	5.5		
4	35		191	78	2.06	6.1		
5	26		181	76.3	1.96	5.9		
6	30		182	94.5	2.16	4.9		
7	33		174	65.5	1.79	5.9		
8	36		190	105	2.33	6.5		
9	34		182	64.8	1.84	5.5		
10	27		184	84.3	2.07	5.5		
Mean ± SD	32.1 ± 3.5		182 ± 5.4	78.9 ± 13.1	2.00 ± 0.17	5.6 ± 0.5		

^a Female

tion the next day, no drink containing methylxanthine was allowed. The subjects were not fasting and the diabetic patients had their usual doses of insulin. On the day of investigation, the first clearance period was started at 08.00 h followed by a second period from 10.45 to 12.45 h. During examination all subjects were in the supine position (only briefly standing or sitting during voiding of urine), and 300 ml of tap-water was given by mouth every hour. Venous blood samples for analysis of glucose, sodium and lithium were drawn at 08.45 h and at the end of each clearance period.

Methods

The GFR was determined from the total ⁵¹Cr-EDTA plasma clearance measured by a simplified single injection method [18] with venous blood sampling 180, 200, 220 and 240 min after intravenous injection of 100 µCi ⁵¹Cr-EDTA at 08.45 h. The minor inaccuracy of clearance versus GFR was corrected for [19] and the thus determined GFR gives a reliable measure of the true GFR in the individual subject [20].

In each of the two clearance periods the renal plasma clearance of lithium (Cl_{Lith}) was calculated as the ratio between the urinary excretion rate and the interpolated serum concentration value at the middle of the clearance period after correction for delay time [21]. Lithium in serum and urine was determined by flame emission spectrophotometry. Due to background emission and ion interference from sodium, potassium and calcium, the determination of lithium in urine by flame emission photometry may give wrong results [22]. To overcome this problem a correction-matrix considering these type of errors was constructed. In urine samples covering the whole range of sodium, potassium and calcium concentrations, as measured by standard methods in the present series of healthy and diabetic subjects, the recovery of lithium was found to be 1.01 ± 0.02 (mean ± SD; range 0.5–4.0 mmol/l), using the correction matrix. The range of corrected lithium concen-

tration in the present study was 0.63–3.00 mmol/l. There was no significant difference between Cl_{Lith} in the two periods in the control or diabetic subjects. The precision of a single Cl_{Lith} determination was 12% (coefficient of variation). Plasma sodium was determined by flame emission photometry on an autoanalyzer (SMA 6/90, Technicon, Tarrytown, USA). Plasma and urinary glucose were determined enzymatically by the glucose-dehydrogenase method on a single channel autoanalyzer (Technicon).

The absolute reabsorption rate in the proximal tubules (ml/min) was determined as GFR·Cl_{Lith}, and the fractional reabsorption rate in the proximal tubules (%) was calculated as (1–Cl_{Lith}/GFR) × 100. The distal reabsorption rate of sodium (mmol/h) was calculated as the difference between Cl_{Lith} multiplied with the plasma sodium concentration and the urinary excretion rate of sodium, and the distal fractional reabsorption rate of sodium (%) was determined as the absolute reabsorption rate divided by Cl_{Lith} multiplied with the plasma sodium concentration. The results are given as the weighted mean of two determinations (one in each clearance period). The values of urinary excretion rate of sodium, GFR, Cl_{Lith} and the absolute reabsorption rates in the proximal and distal tubules were all corrected to a standard surface area of 1.73 m². Body surface area was estimated according to the formula of DuBois and DuBois [23]. Mann-Whitney's non-parametric test was used for comparison of mean values between diabetic and control subjects. A *p* value < 0.05 was considered significant.

Results

GFR in the diabetic patients was significantly increased compared with the control subjects (136 ± 10.2 versus 108 ± 13.6 ml/min, *p* < 0.001), whereas the renal plasma

Table 2. GFR, renal plasma clearance of lithium (Cl_{Li}), reabsorption rates in proximal and distal tubules, plasma sodium concentration and urinary excretion rates in 11 diabetic patients and 10 healthy subjects

Subjects	GFR (ml/min)	Cl _{Lith} (ml/min)	Proximal reabsorption		Distal reabsorption of sodium		Plasma Na (mmol/l)	Urinary Na (mmol/h)	Urine flow (ml/min)
			Fractional (%)	Absolute (ml/min)	Fractional (%)	Absolute (mmol/h)			
Diabetic patients									
1	126	19.9	84.2	106.1	90.0	147	137	16.3	6.1
2	136	29.6	78.2	106.4	96.2	241	141	9.6	4.8
3 ^a	139	28.3	79.6	110.7	93.2	223	141	16.2	7.3
4	128	34.1	73.4	93.9	94.0	260	135	16.8	3.8
5	138	29.9	78.3	108.1	95.1	235	138	12.1	4.7
6	124	31.9	74.3	92.1	95.0	253	139	13.3	4.6
7	161	29.6	81.6	131.4	93.4	227	137	16.0	6.5
8	138	28.1	79.6	109.9	93.3	219	139	15.7	2.7
9	139	30.5	78.1	108.5	94.5	242	140	14.2	5.5
10	142	32.5	77.1	109.5	97.1	259	137	7.8	5.5
11	129	23.7	81.6	105.3	96.6	192	140	6.8	2.3
Mean ± SD	136 ± 10.2	28.9 ± 4.0	78.7 ± 3.2	107.4 ± 10.1	94.4 ± 2.0	227 ± 33	139 ± 1.9	13.2 ± 3.6	4.9 ± 1.5
Normal subjects									
1	86	28.0	67.4	58.0	94.6	224	141	12.7	4.1
2	97	26.2	73.0	70.8	95.4	209	139	10.0	3.8
3	106	30.6	71.1	75.4	96.4	250	141	9.3	3.2
4	106	23.8	77.5	82.2	92.9	188	142	14.3	3.4
5	113	25.8	77.2	87.2	96.0	208	140	8.5	4.4
6	116	40.4	65.2	75.6	95.5	317	137	15.1	8.0
7	93	25.1	73.0	67.9	95.6	197	137	9.1	6.1
8	111	28.0	74.8	83.0	93.4	215	137	15.2	6.1
9	128	22.9	82.1	105.1	93.1	175	137	13.0	4.3
10	126	31.8	74.8	94.2	95.8	254	139	11.3	4.9
Mean ± SD	108 ± 13.6	28.3 ± 5.1	73.6 ± 4.9	79.9 ± 13.6	94.9 ± 1.3	224 ± 41	139 ± 1.9	11.8 ± 2.5	4.8 ± 1.5
<i>p</i>	<0.001	NS	<0.02	<0.001	NS	NS	NS	NS	NS

^a Female

clearance of lithium (Cl_{Li}), did not differ between the two groups (Table 2). The fractional reabsorption rate in the proximal tubules was significantly elevated in the diabetic compared with the control subjects (78.7 ± 3.2 versus $73.6 \pm 4.9\%$, $p < 0.02$), and the same held true for the absolute reabsorption rate in the proximal tubules (107.4 ± 10.1 versus 79.9 ± 13.6 ml/min, $p < 0.001$, Table 2). The absolute and fractional reabsorption rate of sodium in the distal tubules, plasma sodium concentration, urinary excretion rate of sodium and urine flow did not differ between diabetic and control subjects. (Table 2)

Discussion

This study, performed in comparable groups with respect to age and body size of healthy and Type 1 diabetic adults, showed that mean GFR in the diabetic patients was significantly increased compared with the mean value in the control subjects (28 ml/min), whereas the mean flow of fluid from the proximal tubules into the thin descending limb of the loop of Henle did not differ between the two groups. These results indicate

that the elevation of GFR in diabetic patients, as a group, is associated with an identical increase in the proximal reabsorption rate (the present increase being 27.5 ml/min), and with it the proximal fractional reabsorption rate of sodium and water is elevated. This type of glomerulo-tubular balance implies that the flow of water and flux of sodium to the segments distal to the proximal tubule is kept unchanged during variations of GFR, and if at the same time the urinary excretion rate of sodium is unaltered, as in the present study, the fractional and absolute reabsorption rate of sodium in the distal tubules is also kept constant. These results differ from those reported for single-nephrons in animal studies where variations of GFR are associated with *proportional* but not parallel changes of the proximal tubular reabsorption rate [7, 9–13], and with it, the distal reabsorption of sodium varies to keep the final output of sodium unchanged. The results of the present study, however, concern the *whole* kidney in different individuals. To assess more precisely the glomerulo-tubular balance in diabetic patients, further investigations are needed with simultaneous determination of GFR and the renal plasma clearance of lithium at different levels of GFR in the same subject, e.g. in the course of strict

insulin treatment in newly diagnosed diabetic patients during which GFR declines rapidly toward normal values [24, 25].

The glomerulo-tubular balance of glucose and phosphate has been studied previously in patients with Type 1 diabetes of short duration. In the study by Mogensen [26], the maximal reabsorption rate for glucose was found to be increased to the same extent as GFR, whereas the capacity for reabsorption of phosphate was depressed in relation to GFR during non-optimal control of the blood glucose level [27, 28]. The results of these studies, and those of the present investigation, indicate that the glomerulo-tubular balance is preserved for glucose but not for phosphate, whereas it is of a special type for water and sodium in Type 1 diabetic patients with elevated GFR.

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