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Originals

Early glomerular hyperfiltration and the development of late nephropathy in Type 1 (insulin-dependent) diabetes mellitus

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Summary. We performed a follow-up study of the glomerular function in a series of 29 Type 1 (insulin-dependent) diabetic patients who had been studied 18 years previously. Initial median duration of diabetes was 2 years (range 0-9) and at follow-up 21 (17-27) years. At follow-up, 8 diabetic patients exhibited increased urinary albumin excretion rate 515 (32-3234) μg/min with glomerular filtration rates significantly lower than 21 diabetic patients with normal urinary albumin excretion (85 vs 126 ml/min/1.73 m^2; $p < 0.01$). The patients with increased urinary albumin excretion rate also had higher arterial blood pressure (145/90 vs 120/80) mm Hg; $p < 0.02$) and increased frequency of proliferative retinopathy (7 out of 8 vs 2 out of 21; $p = 0.0001$) as compared to the group with normal urinary albumin excretion. However, we found no association of increased urinary albumin excretion rate (incipient or overt nephropathy) to early glomerular hyperfiltration as median initial glomerular filtration rate was 142 ml/min/1.73 m^2 in the diabetic patients with increased urinary albumin excretion and 147 ml/min/1.73 m^2 in the patients with normal excretion rate ($p > 0.05$)

Key words: Glomerular filtration rate, Type 1 (insulin-dependent) diabetes, microalbuminuria, diabetic nephropathy.

Increased glomerular filtration rate (GFR) is a well established feature of early uncomplicated Type 1 (insulin-dependent) diabetes [1-5]; changes in glomerular haemodynamics (increased transcapillary pressure and flow) are believed to be important for the development of diabetic glomerular injury [6-8]. Based on studies in animals with experimental diabetes it has been proposed that elevated GFR in early stages of the disease might predict the later development of nephropathy [9, 10]. This suggestion has recently been supported by findings in patients with Type 1 diabetes [11, 12]. Because of the potential importance of being able to identify patients at risk for developing end-stage renal failure we decided to perform a follow-up study of the kidney function in a series of Type 1 diabetic patients who had been studied 18 years previously.

Subjects and methods

Selection of patients

As a result of growing interest in the late 1960s of identifying renal hyperfiltration in short-term diabetic patients, GFR was measured in 73 diabetic patients referred to our medical department from 1967 to 1969. Fifty-one of the 73 diabetic patients were considered to have Type 1 diabetes. As part of a retrospective study 37 diabetic patients were selected for re-examination as they fulfilled the following criteria: (1) Males and females with Type 1 diabetes (2) Age at onset less than 40 years (3) Duration of diabetes at initial examination less than 10 years (4) None had clinical proteinuria (> 0.5 g per 24 h) or diabetic retinopathy and (5) GFR and renal plasma flow (RPF) had concomitantly been measured at the initial examination. Eight out of the 37 selected patients could, however, for the following reasons not be re-examined. Four patients had died (2 of diabetic nephropathy, see Table 3), 2 could not be found through the central population registry, and 2 refused re-examination.

Initial examination

Initial and follow-up clinical features including some paraclinical data are shown in Tables 1, 2 and 3. Median age of the total 37 diabetic patients (21 males and 16 females) was 24 (range 11-39) years with a diabetes duration of 2 (< 1-9) years. Nine of the 37 patients had newly diagnosed diabetes at the initial examination; one was examined prior to insulin treatment, while the remaining 8 diabetic patients were investigated 8 [1-14] days after starting insulin treatment. Twenty-eight of the 37 diabetic patients had a duration of diabetes greater than 6 months. No effort was made to obtain a strict normalisation of the blood glucose. One newly-diagnosed diabetic patient and one with longer duration of the disease were mildly ketotic with serum bicarbonate 19.2 mmol/l (case no. 10) and 18.0 mmol/l (case no. 13) respectively. None of the patients had symptomatic hypoglycaemia during the examination. Besides having diabetes the patients were healthy and received no medication other than insulin.

Table 1. Clinical features and some paraclinical data of the 29 re-examined diabetic patients

Case no.	Sex	Age (years)	Duration of diabetes (years)		Insulin dose (IU)		Body surface area (m^2)		Blood pressure (mm Hg)		Blood glucose (mmol/l)		HbA_{1c} (%)
		Initial	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up	Follow-up
1	M	15	4	25	40	76	1.66	2.02	120/75	120/65	–	8.7	6.3
2	M	17	9/12	22	44	40	1.79	1.99	105/75	110/75	–	12.8	6.7
3	M	22	4	22	48	44	1.82	1.87	120/80	140/80	6.7	14.9	6.9
4	M	30	6	24	40	52	1.88	2.01	130/85	145/90	2.2	12.6	7.2
5	M	20	5	24	48	40	1.79	1.85	110/80	125/80	6.4	11.0	6.7
6	M	25	2	21	28	44	1.72	1.85	115/70	130/80	10.3	16.1	7.6
7	M	33	7	25	48	46	1.75	1.84	145/80	110/75	8.7	13.7	7.6
8	M	14	ND[a]	18	20	56	1.34	1.96	115/60	160/90	15.0	16.9	8.9
9	M	15	6	24	68	48	1.72	2.01	120/80	140/90	17.2	14.7	10.7
10	M	31	2	21	24	24	1.63	1.62	125/85	140/70	13.3	8.2	9.0
11	M	31	ND	18	20	40	1.98	2.08	120/80	160/90	8.9	18.1	8.6
12	M	27	9	27	28	44	2.09	2.12	140/85	150/90	9.7	13.4	7.2
13	M	39	ND	17	20	50	1.73	2.03	125/75	160/90	13.3	16.5	10.1
14	M	25	ND	17	36	52	1.80	1.88	135/85	130/80	5.1	11.7	9.7
15	M	21	9/12	18	36	44	1.76	1.96	110/80	140/85	10.7	12.8	8.4
16	M	39	8	25	52	40	1.86	1.80	110/70	135/70	10.5	13.4	9.8
17	M	15	4	24	60	36	1.80	2.14	110/60	100/70	11.8	13.3	9.2
18	F	24	6	26	48	44	1.59	1.82	110/85	140/90	9.8	33.0	11.5
19	F	16	2	21	36	44	1.66	1.74	120/70	130/80	3.9	15.4	12.3
20	F	12	7	27	36	24	1.24	1.45	120/80	120/60	11.4	18.4	9.4
21	F	11	1	21	32	60	1.18	1.67	115/80	110/80	15.8	15.6	6.9
22	F	34	1	19	20	32	1.65	1.76	110/70	110/70	13.9	9.6	7.3
23	F	15	4	23	56	50	1.53	1.72	115/80	105/65	10.6	11.5	8.2
24	F	16	2	20	56	58	1.75	1.80	110/70	120/80	5.8	20.8	14.1
25	F	18	9	26	72	34	1.65	1.69	135/85	140/75	4.2	11.6	8.6
26	F	14	7	26	80	50	1.68	1.96	120/75	155/100	10.1	5.9	9.9
27	F	15	ND	18	0	32	1.36	1.60	110/60	105/75	14.1	7.8	6.8
28	F	32	ND	18	24	50	1.66	1.69	105/70	110/65	5.9	2.9	7.2
29	F	20	ND	18	12	20	1.55	1.70	110/70	120/80	7.7	17.2	11.5
median		20	2	22	36	44	1.72	1.85	120/80	130/80	10.1	13.4	8.6

[a] Newly-diagnosed

All clearance tests were performed in the morning with the subjects in a supine position. Glomerular filtration rate was determined either by constant infusion of inulin (Laevosan Gesellschaft, Linz, Austria) or after a single injection of ^{51}Chromium-EDTA (Radiochemical Centre, Amersham, UK). After a priming dose of inulin (in 7 out of the 37 diabetic patients), a sustaining infusion was given allowing an equilibration period of not less than 30 min. Three consecutive clearance tests were carried out in each patient. Urine was collected at the end of each test and blood specimens were drawn in the middle of each test. The ^{51}Chromium-EDTA clearance (in 30 out of the 37 diabetic patients) was calculated from the plasma disappearance curve studied for at least 4 h after a single intravenous injection of 3.7 MBq ^{51}Chromium-EDTA by taking venous blood samples every 5 min up to 30 min and thereafter every 30 min. Previous comparison in this department of ^{51}Chromium-EDTA- and inulin clearances in 33 patients has shown good agreement with a regression line: ^{51}Chromium-EDTA = 0.84 x inulin + 12.27 ($r = 0.97$) [13]. For comparison the initial ^{51}Chromium-EDTA clearance values were corrected according to this equation and the standard body surface area of 1.73 m^2. RPF was measured either by the para-aminohippurate clearance method [14] or by ^{125}I-hippuran [15]. Comparison in this laboratory of these two methods in 20 patients with normal and impaired renal function showed good correlation and therefore the ^{125}I-hippuran clearance values were corrected according to the equation: para-aminohippurate = 1.132x^{125}-I-hippuran + 14.24 ($r = 0.99$) [2].

A control group examined between 1967 and 1969 was included in the study. The data of the 29 control subjects (13 males and 16 females) are shown in Table 4. The median age was 30 [17-39] years. Suspected or known diagnoses during the hospital stay were previous epigastric pain in 9 subjects, irritable bowel syndrome in 2, cephalgia in 1, euthyroid goitre in 2, neurosis in 14 and transient exanthema in 1 subject. The control group were otherwise healthy. Renal function tests were performed as described. GFR was measured by inulin clearance in 11 of the 29 control subjects or by ^{51}Chromium-EDTA clearance in the remaining 18 control subjects. Normal serum creatinine level in our laboratory was less than 140 µmol/l (< 1.3 mg%).

Follow-up examination

The 29 patients (17 males and 12 females) were re-examined after a median period of 18 [17-21] years following the initial examination. Median age was 38 [31-56] years and duration of diabetes 22 [17-27] years. GFR was measured after a single i.v. injection of 3.7 MBq ^{51}Chromium-EDTA (Radiochemical Centre, Amersham, UK.) starting at 09.00 hours [16]. Breakfast and the usual morning insulin dose were allowed. During the clearance study the patients were in a supine position and arterial blood pressure (phase I/V) was recorded with a standard mercury sphygmomanometer on three separate occasions during the clearance test by a trained nurse. Urinary albumin was measured ad modum (Mancini et al., 17) in 3 urine samples collected within one month following each clearance test. Increased urinary albumin excretion rate (UAE) was defined as an excretion rate greater than 20 µg/min in 2 out of 3 sterile timed overnight urine samples [18]. Serum creatinine was analysed using the Jaffe' reaction (normal value in our laboratory: 60-125 µmol/l), serum β_2-microglobulin by a radioimmunoassay (Pharmacia AB, Uppsala, Sweden) (normal range: 70-210 nmol/l) and glycosylated haemoglobin (HbA_{1c}) (normal range: 3.5-6.2%) was measured by a chromatographic method [19].

Table 2. Paraclinical data on the 29 re-examined diabetic patients

Case no.	Glomerular filtration rate (ml/min/1.73 m^2)		Renal plasma flow (ml/min/1.73 m^2)	Filtration fraction	Serum-creatinine (μmol/l)		S-β_2-microglobulin (nmol/l)	Urinary Albumin excretion rate (μg/min)	Retinopathy[a]	Antihypertensive treatment[b]
	Initial	Follow-up	Initial	Initial	Initial	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up
1	157	119	693	0.23	90	99	127	9	S	
2	143	105	806	0.18	102	96	177	527	–	
3	116	107	577	0.20	136	100	128	6	S	
4	121	110	544	0.22	113	104	122	8	S	
5	156	143	739	0.21	79	99	129	1	P	
6	148	165	847	0.17	79	82	118	5	P	
7	133	125	700	0.19	79	84	–	3	S	
8	122	83	499	0.24	124	126	158	1125	P	
9	171	128	672	0.25	113	91	147	502	P	
10	151	126	631	0.24	113	82	102	3	S	
11	135	132	648	0.21	113	91	111	13	S	
12	140	87	687	0.20	113	113	206	71	P	AF
13	158	102	607	0.26	102	95	151	32	P	
14	127	141	736	0.17	90	80	125	5	–	
15	134	147	680	0.20	79	76	138	10	–	
16	132	32	666	0.20	102	211	476	3234	P	
17	150	112	740	0.19	102	81	133	12	S	
18	117	53	649	0.18	79	117	255	250	P	B
19	119	122	673	0.18	79	92	98	8	S	
20	159	118	598	0.27	79	75	90	13	S	
21	165	132	578	0.29	136	84	111	9	–	
22	128	88	611	0.21	79	76	129	5	–	
23	150	141	838	0.18	68	64	111	15	–	
24	169	152	724	0.23	57	69	103	7	S	
25	147	120	655	0.22	90	80	111	7	S	
26	170	68	749	0.23	68	100	195	2170	P	T
27	125	103	630	0.20	102	72	137	6	S	
28	147	142	547	0.27	79	54	158	6	S	
29	193	135	706	0.27	57	81	93	7	–	
median	147	120	672	0.21	90	84	129	9		

[a] Retinopathy was either of (S)simplex or (P)proliferative type; [b] A: angiotensin converting enzyme inhibitor, B: selective β-blocking agent; F: furosemide; T: thiazide

Statistical analysis

Values are expressed as median with range. Test for significance was assessed non-parametrically using the Mann-Whitney test, the Fisher test or when appropriate the Spearman rank correlation coefficient (rho); 5% was chosen as the level of statistical significance.

Results

Initial examination

Initial examination of renal function in the 37 Type 1 diabetic patients (Tables 2 and 3) as compared to 29 healthy control subjects (Table 4) showed that both median GFR [144(112–193) ml/min/1.73 m^2 vs 125(95–173) ml/min/1.73 m^2; $p < 0.002$] and filtration fraction (defined as GFR divided with RPF) [0.21(0.16–0.29) vs 0.18(0.11–0.23); $p < 0.0001$] were significantly increased in the diabetic patients. In the 8 patients not examined at follow-up the median GFR [141(112–171) vs 147(116–193) ml/min/1.73 m^2], RPF [667(563–936) vs 672(499–847) ml/min/1.73 m^2] and filtration fraction [0.22(0.16–0.24) vs 0.21(0.17–0.29)] did not differ significantly from those of the remaining 29 diabetic patients. Nor was there found any significant difference between the median GFR [135(122–193) vs 147(112–171) ml/min/1.73 m^2], RPF [630(499–736) vs 677(544–936) ml/min/1.73 m^2] and filtration fraction [0.22(0.17–0.27) vs 0.21(0.16–0.29)] in the 9 newly diagnosed Type 1 diabetic patients and the 28 patients with a duration longer than 6 months. In the two diabetic patients with serum bicarbonate below the lower normal limit initial GFR were 151 ml/min/1.73 m^2 (case no. 10) and 158 ml/min/1.73 m^2 (case no. 13). Initial GFR of the 2 patients dying from nephropathy (case nos. 32,37) were 144 and 112 ml/min/1.73 m^2 respectively. Duration of diabetes was not longer in the 8 patients not examined at follow-up as compared to the 29 diabetic patients participating in the follow-up examination. In both this group and in the 9 newly-diagnosed patients no significant difference was found between fasting blood glucose, insulin dose, body surface area or blood pressure as compared to the remaining diabetic patients.

Table 3. Initial clinical features and some paraclinical data of the 8 diabetic patients not re-examined

Case no.	Sex	Age (years)	Duration of diabetes (years)	Insulin dose (IU)	Body surface area (m^2)	Blood pressure (mm Hg)	Blood-glucose (mmol/l)	Serum-creatinine (μmol/l)	Glomerular filtration rate (ml/min/1.73 m^2)	Renal plasma flow (ml/min/1.73 m^2)	Filtration fraction
30	M	28	4	56	1.63	125/75	8.2	124	147	936	0.16
31	M	30	ND[a]	32	1.54	120/70	6.8	113	124	563	0.22
32[b]	M	32	ND	20	1.70	135/95	9.2	136	144	678	0.21
33[c]	M	34	5	40	1.66	120/75	10.7	79	138	615	0.22
34	F	37	6/12	28	1.58	100/65	13.4	68	171	725	0.24
35[d]	F	36	8	32	1.69	115/80	15.8	79	129	744	0.17
36	F	24	6	40	1.54	125/70	9.0	68	147	655	0.22
37[b]	F	20	2	32	1.66	120/80	4.9	90	112	561	0.20
median		31	3	32	1.65	120/75	9.1	85	141	667	0.22

[a] Newly-diagnosed. Died from [b] diabetic nephropathy; from [c] bronchogenic carcinoma; [d] ischaemic heart disease during follow-up period

Table 4. Clinical features and paraclinical data of 29 control subjects investigated from 1967-1969

Case no.	Sex	Age (years)	Body surface area (m^2)	Blood pressure (mm Hg)	Serum-creatinine (μmol/l)	Glomerular filtration rate (ml/min/1.73 m^2)	Renal plasma flow (ml/min/1.73 ^{2})	Filtration fraction
38	F	26	1.44	120/70	90	137	1168	0.12
39	F	21	1.60	110/75	90	129	1005	0.13
40	F	25	1.48	110/70	79	142	753	0.19
41	F	25	1.84	125/85	124	127	784	0.16
42	F	34	1.86	130/90	113	95	491	0.19
43	F	36	1.58	115/75	102	128	638	0.20
44	F	33	1.60	120/70	102	150	639	0.23
45	F	35	1.73	140/75	90	119	568	0.21
46	F	25	1.54	110/75	90	154	698	0.22
47	F	17	1.46	105/80	102	95	492	0.19
48	F	35	1.48	130/90	68	173	947	0.18
49	F	22	1.36	110/70	102	109	731	0.15
50	F	35	1.36	110/80	102	95	452	0.21
51	F	22	1.88	110/80	102	96	709	0.14
52	F	31	1.52	110/70	113	102	575	0.18
53	F	23	1.44	105/60	90	118	888	0.13
54	M	39	1.66	130/65	90	117	695	0.17
55	M	38	1.61	125/65	102	137	993	0.14
56	M	20	1.73	140/85	124	124	1105	0.11
57	M	28	1.86	130/70	102	114	855	0.13
58	M	24	1.57	110/60	136	125	862	0.15
59	M	30	1.80	115/70	102	106	709	0.15
60	M	36	1.60	110/70	124	120	701	0.17
61	M	24	1.92	130/85	102	168	914	0.18
62	M	37	1.70	120/80	79	146	730	0.20
63	M	38	1.78	115/70	79	143	611	0.23
64	M	30	1.77	130/90	124	107	481	0.22
65	M	24	1.74	120/80	113	144	706	0.20
66	M	36	1.90	125/85	113	125	742	0.17
median		30	1.61	120/75	102	125	709	0.18

Follow-up examination

The 29 diabetic patients were divided into two groups according to their urinary excretion rates. In the 8 patients with elevated UAE the median value was 515(32-3234) μg/min and was clearly separated from the 21 diabetic patients with normal UAE. Seven out of 8 had values of UAE greater than 71 μg/min. Both median blood pressure (145/90 mm Hg vs 120/80 mm Hg; $p < 0.02$) and the frequency of proliferative retinopathy (7 out of 8 vs 2 out of 21; $p = 0.0001$) were significantly increased among the patients with abnormal UAE as compared to the group with normal UAE. Three out of the 29 diabetic patients (all with increased UAE) received antihypertensive treatment.

No significant correlation was found between UAE and initial GFR (Spearman rho = 0.095; $p > 0.05$) (Fig. 1). The median initial GFR was 142(117-170) ml/min/1.73 m^2 in the diabetic patients with increased UAE as compared to 147(102-193) ml/min/1.73 m^2 in

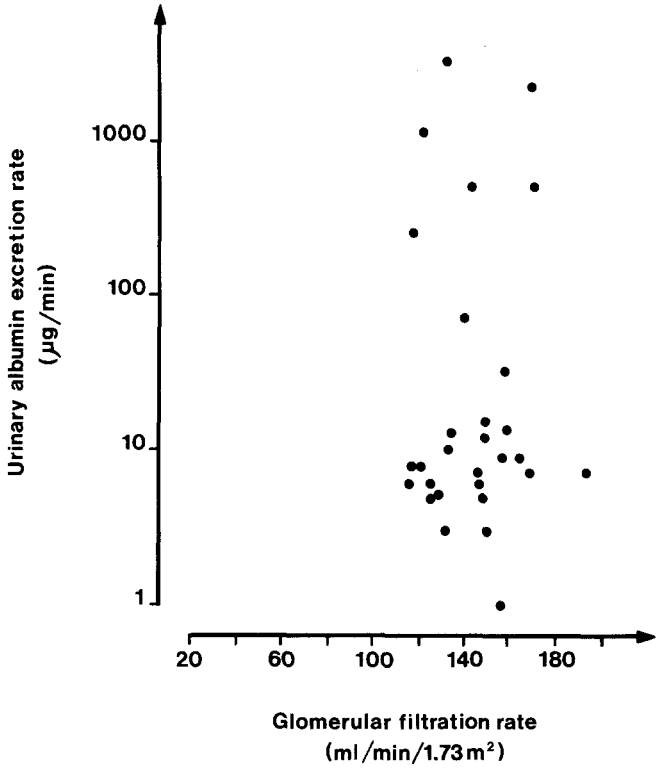

Fig. 1. Urinary albumin excretion rate (log scale) in 29 diabetic patients plotted against glomerular filtration rate at initial examination (Spearman rho = 0.095; $p > 0.05$)

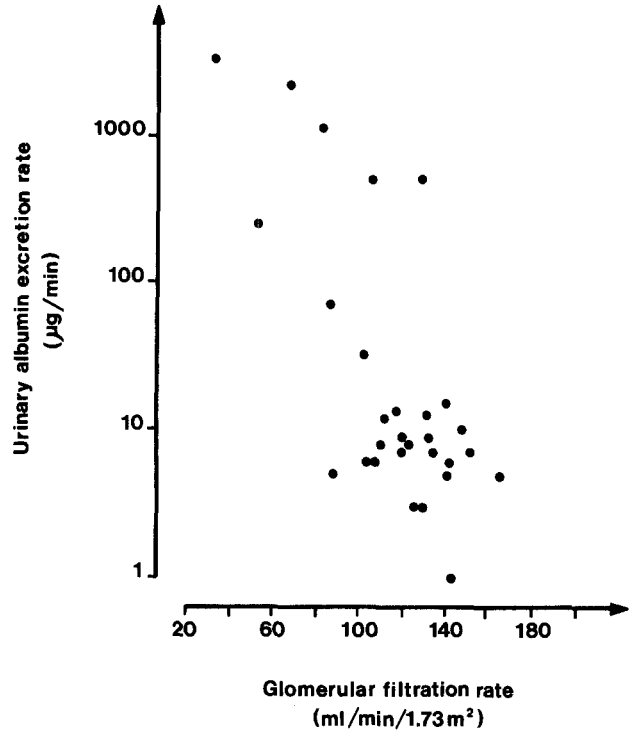

Fig. 2. Urinary albumin excretion rate (log scale) in 29 diabetic patients plotted against glomerular filtration rate at follow-up examination (Spearman rho = −0.536; $p < 0.01$)

the patients with normal UAE. Nor were there any significant relationships between increased UAE and the initially determined RPF or filtration fraction. However, UAE was negatively correlated with follow-up GFR as shown in Figure 2 (Spearman rho = −0.536; $p < 0.01$). GFR at follow-up was decreased in the group with abnormal UAE as compared to the diabetic patients with normal albumin excretion [85(32-128) vs 126(88-165) ml/min/1.73 m^2; $p < 0.01$]. The diabetic patients with increased UAE had higher serum creatinine levels [107(91-211) µmol/l vs 81(54-104) µmol/l; $p < 0.01$] and higher serum β_2-microglobulin levels [186(147-476) nmol/l vs 120(93-158) nmol/l; $p < 0.01$] as compared to patients with normal UAE. The groups were similar with respect to age, duration of diabetes, insulin dose, body surface area, blood glucose and HbA_{1c}.

Discussion

Duration of disease is the major susceptibility factor for the development of diabetic retinopathy and nephropathy. Though most diabetic patients suffer from some structural and functional changes in the kidney glomeruli even early in the disease it still remains unexplained why only approximately one-third of the patients progress to diabetic nephropathy and renal failure [20].

Microalbuminuria strongly predicts diabetic nephropathy, the progression of which may be reduced by continuous subcutaneous infusion of insulin [21] and by early antihypertensive treatment [22, 23]. However, once macroalbuminuria appears the fatal outcome is predictable [20, 24]. Therefore, a crucial goal in prevention would be to demonstrate factors early during the disease which may indicate the development of renal failure in the individual patient.

Based on single-nephron micropuncture studies in experimental diabetic rats it has been supposed that glomerular hyperfiltration, resulting from concomitant elevations in glomerular flow and pressure, might be an early marker of subsequent renal damage [6-8]. Recent findings by Mogensen in Type 1 diabetic patients [11, 12] tends to support this hypothesis. In both latter clinical studies renal function was reinvestigated in, respectively, 24 and 12 male diabetic patients; a significant association was found between early glomerular hyperfiltration and development of late nephropathy. In our study no association was demonstrable between early elevated glomerular filtration rate (or increased filtration fraction) and late incipient or overt nephropathy. Nor were such associations found when males or female diabetic patients were analysed separately.

The reason for the different results found by Mogensen and the present study may be due to several factors. The diabetic patients in the studies by Mogensen had a mean age at diagnosis of 12 and 14 years, re-

spectively, as compared to the mean age of 19 years in our study; and the initial mean duration of diabetes were 12 and 6 years as compared to 3 years in the present study. The mean follow-up periods were only 10 and 13 years in the studies by Mogensen in contrast to 19 years in the present study, and this longer follow-up period might have given rise to an increased frequency of patients with nephropathy. The short-term regulation of diabetes in the 3 studies may be different, although the mean blood glucose levels appear to be similar. The long-term quality of metabolic control of the diabetic patients in the 3 studies cannot be compared because of insufficient accumulation of data within the follow-up period. The determination of glycosylated haemoglobin was not a routine laboratory method at the initial examination and for several years thereafter. The methodology used for the GFR determinations was also different as Mogensen used iothalamate or inulin as filtration markers at the initial examination, while we used ^{51}Chromium-EDTA or inulin with correction of the former. In the studies by Mogensen microalbuminuria were present in many of the diabetic patients even at the initial examination and from their studies it is, therefore, not possible to establish whether hyperfiltration per se may predict late renal failure. We did not have the possibility of measuring microalbuminuria at the initial examination in 1967.

The finding by Mogensen and Christensen [11] of a significantly higher blood pressure initially in the group of diabetic patients who subsequently developed nephropathy at follow-up could not be confirmed either by Mogensen [12] or in the present study. However, as might be expected, we found a higher blood pressure and an increased frequency of proliferative retinopathy at follow-up in the diabetic patients with increased urinary albumin excretion rates [25, 26].

Although experimental evidence suggest that increased GFR is linked to intrarenal hypertension and progressive renal damage, the verification of this hypothesis in human diabetes is probably difficult to establish. As several factors such as dietary protein-intake [27, 28], metabolic control of diabetes [29–31] and plasma levels of various endogenous hormones [32–34] are known reversibly to influence the level of GFR, future studies of GFR must be carried out prospectively with due consideration of these variables.

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