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Kidney function in newly diagnosed Type 2 (non-insulin-dependent) diabetic patients, before and during treatment

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Summary. Glomerular filtration rate, kidney volume, and urinary albumin excretion rate were studied in otherwise healthy newly diagnosed Type 2 (non-insulin-dependent) diabetic patients, untreated at diagnosis, after short-term treatment and after 3 months treatment. In 10 patients (Group A) glomerular filtration rate (measured by the plasma clearance of 51-Cr-EDTA) decreased from the time of diagnosis 106.2 ± 14.6 ml · min^{-1} · 1.73 m$^{2-1}$ (mean ± SD) to 95.9 ± 13.7 ml · min^{-1} · 1.73 m$^{2-1}$ after 3 months treatment ($p = 0.049$). At the same time, mean plasma glucose was reduced from 13.3 ± 3.2 mmol/l to 6.5 ± 1.1 mmol/l. The fall in mean plasma glucose was correlated to the reduction in glomerular filtration rate, $r = 0.76$, $p = 0.011$. Kidney volume as measured by ultrasonic scanning was reduced from 264.0 ± 33.7 ml/1.73 m^2 to 210.8 ± 23.8 ml/1.73 m^2 ($p < 0.005$). The relative decline in urinary albumin excretion rate was correlated to the fall in glomerular filtration rate, $r = 0.69$, $p = 0.026$. In 15 patients (Group B) 24-h urine collections were made during 9.5 ± 3.2 days, urinary albumin excretion rate fell from the first to the last day in hospital from $14.0 \times /\div 3.0$ μg/min (geometric mean $\times /\div$ tolerance factor) to $7.0 \times /\div 2.7$ μg/min $p = 0.015$. The relative decline was correlated to the change in mean plasma glucose, $r = 0.65$, $p = 0.032$.

Thus, kidney function in Type 2 diabetic patients is influenced by metabolic control, although to a lesser extent than is seen in Type 1 (insulin-dependent) diabetic patients with comparable glycaemic control. Urinary albumin excretion is reduced by improvement in glycaemic control, to which it is significantly correlated. Long-term consequences of reduction in urinary albumin excretion on the development of diabetic nephropathy and on survival remains to be elucidated.

Key words: Type 2 (non-insulin-dependent) diabetes, kidney function, glomerular filtration rate, kidney volume, urinary albumin excretion, newly diagnosed diabetes, glycaemic control, HbA_{1c}.

Renal hypertrophy and hyperfiltration are characteristic and well described findings in Type 1 (insulin-dependent) diabetes, present at diagnosis and lasting for many years [1-4]. The exact causative mechanisms behind this hyperfunction is unknown [3]. Earlier studies have demonstrated that improvement in glycaemic control reduces glomerular filtration rate (GFR) as well as kidney size in short-term Type 1 diabetes but with still supranormal values [3, 5]. Microalbuminuria i.e. urinary albumin excretion rate (UAE) from 20-200 μg/min [6] is often present at diagnosis and is normalized by insulin treatment [7, 8]. This initial reversible microalbuminuria is contrasted by the persisting and increasing microalbuminuria which predicts the development of diabetic nephropathy [9, 10].

In Type 2 (non-insulin-dependent) diabetes studies are fewer, but renal hyperfunction and nephromegali do not seem to be common features [11-13]. Microalbuminuria is frequent in Type 2 diabetes and has been demonstrated also in newly diagnosed subjects [12, 14]. In Type 2 diabetes, microalbuminuria predicts the development of clinical proteinuria [15] and early mortality [15-17].

To our knowledge no previous studies on the effect of glycaemic control on GFR and kidney volume (KV) have been carried out in Type 2 diabetic patients.

The aim of the present investigation was, in newly diagnosed Type 2 diabetic patients, to study the impact of glycaemic control on GFR, KV as well as UAE.

Subjects and methods

The protocol comprised two issues: A) GFR, KV and UAE were studied in I: the newly diagnosed untreated state on hospital admission, II: after short-term treatment just before discharge and III: after

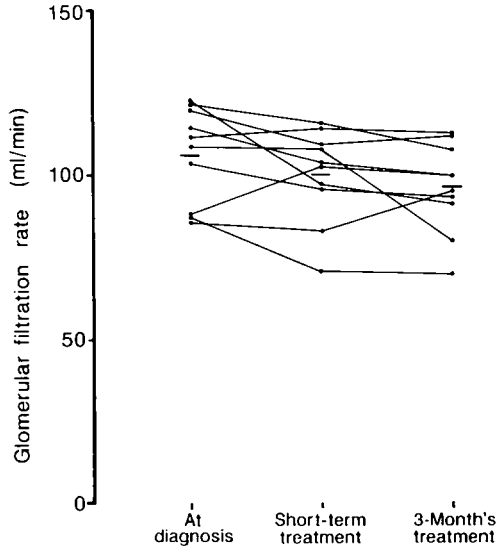

Fig. 1. Glomerular filtration rate (GFR) (adjusted to 1.73 m^2 body surface) in 10 newly diagnosed Type 2 diabetic patients, at diagnosis, during short-term treatment and after 3 months treatment. GFR declined from 106.2 ± 14.6 ml/min (I) to 95.9 ± 13.7 ml/min (III), $p = 0.049$

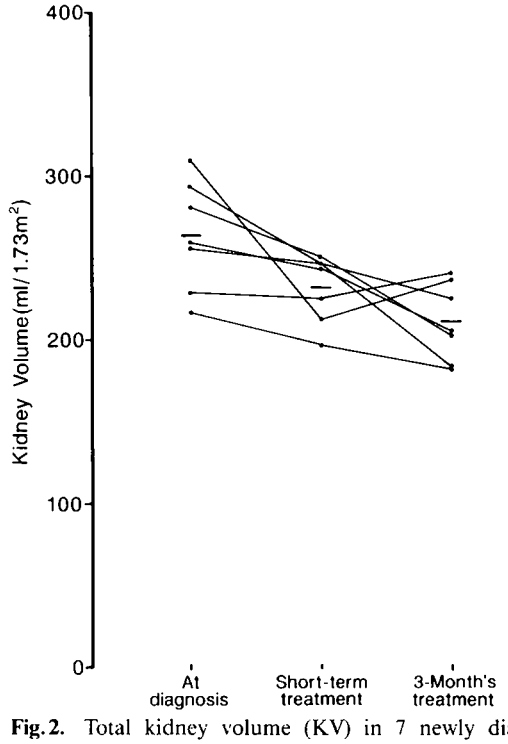

Fig. 2. Total kidney volume (KV) in 7 newly diagnosed Type 2 diabetic patients, at diagnosis, during short-term treatment, and after 3 months treatment. KV was decreased from 264 ± 33.7 ml/1.73 m^2 (I) to 210.8 ± 23.8 ml/1.73 m^2 (III), $p = 0.0046$

3 months treatment. B) Metabolic control and UAE were assessed daily during the stay in hospital and after 3 months of treatment.

A total of 15 patients participated, five of whom accepted only issue B.

Subjects

The patients were recruited consecutively to the study on admission to hospital with newly diagnosed and untreated diabetes and according to the inclusion criteria: age 50–70 years, fasting plasma glucose > 8 mmol/l, fasting C-peptide > 1 ng/ml and/or treatment manageable with diet or oral agents alone. Serum creatinine < 110 µmol/l and no diabetic retinopathy. They were otherwise healthy with no need of medication, on clinical examination there was no sign of cardiac disease, palpable pulse in arteria dorsales pedes and blood-pressure in the supine position was ≤ 160/95 mm Hg. X-ray of the thorax showed no cardiac ectasia and the ECG showed no ischaemic changes.

All the subjects gave their informed consent to the study, which was approved by the local ethical committee, and performed according to the declaration of Helsinki.

The clinical data for the patients appear in Table 1. Three of the patients were treated with diet only and twelve with diet and oral antidiabetic agents.

Methods

GFR was measured as the plasma clearance of 51-Cr-EDTA using the single shot procedure [18] and corrected to 1.73 m^2 surface area. The subjects were investigated resting in the supine position at the same time of day starting at 10.00 hours. Total KV was measured by Ultrasonic scanning [19]. The volume of each kidney was measured twice, and the mean total volume corrected to standard surface area. UAE and beta-2-microglobulin were determined with 24 h urine samples, the albumin concentration was measured by radioimmunoassay [20] and beta-2-microglobulin concentration by ELISA. Urine samples were cultured at investigation I, II and III and were without significant bacteriuria. On admission, fasting plasma C-peptide was measured by a Radioimmunoassay Kit (Inc. Star Corp., Minnesota, USA). HbA_{1c} was measured on admission and after 3 months by cation exchange chromatography [21]. Blood samples for plasma glucose were obtained daily after fasting at 07.30 hours, 11.30 hours and 17.30 hours and measured by standard enzymatic technique. The daily mean was calculated from these three measurements. Blood pressure was measured after 30 min rest in the supine position using a conventional sphygnomanometer, with phase V for diastolic value. The retinal status was judged by a trained ophthalmologist.

Compliance

Study A. All ten patients completed the study. For technical reasons the KV of two patients was not measured on diagnosis. Measurement of KV in one subject with a body mass index of 45.0 kg/m^2 was excluded from calculations due to problems of ultrasonic measurement with extreme obesity.

Table 1. Clinical data for all patients, given as number (n) or mean ± SD and (range)

n	Sex M/F	Age (years)	Fasting plasma glucose (mmol/l)	HbA_{1c} (%)	Fasting plasma C-peptide (ng/ml)	BMI (kg/m^2)	Body surface (m^2)	Blood pressure systolic (mm Hg)	Blood pressure diastolic (mm Hg)	Serum creatinine (µmol/l)	Retinopathy
15	7/8	59 ± 5 (51–68)	13.4 ± 2.8 (8.8–17.2)	9.8 ± 1.3 (7.6–13)	3.2 ± 1.6 (1.4–6.1)	30.3 ± 6.1 (23.5–45.0)	1.91 ± 0.26 (1.61–2.62)	133 ± 16 (110–160)	83 ± 9 (65–95)	79 ± 15 (55–106)	0

BMI: Body Mass Index

Study B. A few inevitable errors of urine collection occurred (1.2 ± 0.9 collections), the days concerned were excluded from calculations. Eleven of the 15 patients had UAE measured at 3 months.

Statistical analysis

Differences between the first (I) and third (III) investigations were judged by Student's t-test for paired observations (two-tailed). Correlations were calculated as r. Unless otherwise indicated UAE and beta-2-microglobulin excretion rates were $\log_{10}$ transformed and mean ± SD (tolerance interval) is therefore given as geometric mean ×/÷ tolerance factor.

Body surface was calculated according to the formula: body surface = weight (kg) $^{0.425}$ × height (cm) $^{0.725}$ × 71.84.

Results

Study A

Mean plasma glucose decreased during the study from 13.3 ± 3.2 mmol/l (mean ± SD) (investigation I) to 8.5 ± 1.6 mmol/l (investigation II) and 6.5 ± 1.1 mmol/l (investigation III). HbA_{1c} (I) decreased from 9.5 ± 0.9% to 6.4 ± 0.6% (III). As shown in Figure 1 there was a moderate but significant decrease in GFR from 106.2 ± 14.6 ml · min^{-1} · 1.73 m$^{2-1}$ (I) to 95.9 ± 13.7 ml · min^{-1} · 1.73 m$^{2-1}$ (III), $p = 0.049$. KV decreased in the seven patients from 264.0 ± 33.7 ml/1.73 m^2 (I) to 210.8 ± 23.8 ml/1.73 m^2 (III), $p = 0.0046$ (Fig. 2). The figures from the extremely obese subject were: 480.9 ml/1.73 m^2 (I), 363.0 ml/1.73 m^2 (II) and 277.5 ml/1.73 m^2 (III). The two subjects investigated at II and III had the volumes: 235.6 ml/1.73 m^2 (II), 224.1 ml/1.73 m^2 (III) and 199.5 ml/1.73 m^2 (II), 258.1 ml/1.73 m^2 (III). The change in KV was not correlated to the change in GFR.

In these 10 patients the UAE from the time of the first GFR measurement to the time of the 3 month's measurement, tended to decrease from 10.5 ×/÷3.6 μg/min to 6.2 ×/÷2.4 μg/min, NS ($p = 0.098$). There was no significant correlation between GFR (I) and UAE (I), ($r = 0.61$, $p = 0.06$), but the change in UAE expressed as the relative decline i.e. UAE I÷UAE III was significantly correlated to the fall in GFR $r = 0.69$, $p = 0.026$ (Fig. 3).

There was no correlation between plasma glucose I and GFR I, but the change in mean plasma glucose was significantly correlated to the decline in GFR ($r = 0.76$, $p = 0.011$) (Fig. 4).

There was neither a correlation between HbA_{1c} I and GFR I nor between their changes. The blood pressure was normal and unchanged. Body surface area decreased from 1.93 ± 0.3 m^2 (I) to 1.85 ± 0.3 m^2 (III).

Study B

24 h urine samples were collected during 9.5 ± 3.2 days in 15 patients. UAE fell between the first and the last day in hospital from 14.0 ×/÷3.0 μg/min to 7.0 ×/÷2.7 μg/min, $p = 0.015$, and in 11 patients from the first day to the 3 month control from 12.3 ×/÷3.4 μg/min to 5.9 ×/÷2.4 μg/min, $p = 0.032$. The relative decline in UAE was significantly correlated to the change in mean plasma glucose ($r = 0.65$, $p = 0.032$). For each individual patient the correlation between the mean plasma glucose and UAE was calculated (Table 2). Of the 15 patients twelve showed a decline in UAE during treatment, the remaining three initially had very low values of UAE and showed only minor increments.

Beta-2-microglobulin excretion rate was unchanged from the first (0.021 ×/÷0.004 μg/min) to the last (0.017 ×/÷0.004 μg/min) day at hospital.

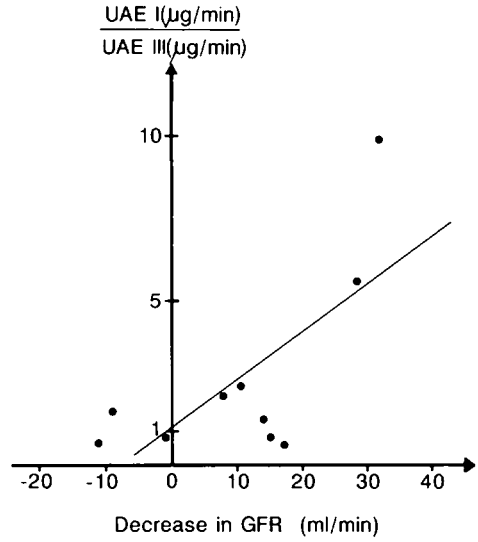

Fig. 3. Decrease in glomerular filtration rate (GFR) (adjusted to 1.73 m^2 body surface) from time of diagnosis (I) to the 3 months investigation (III) versus the relative decline in urinary albumin excretion ($UAE_I \div UAE_{III}$) in 10 newly diagnosed Type 2 diabetic patients. A significant positive correlation was found: $r = 0.69$, $p = 0.026$

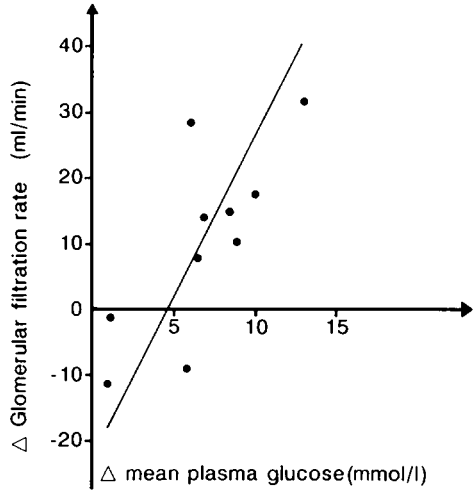

Fig. 4. Δ mean plasma glucose versus Δ glomerular filtration rate (GFR) (adjusted to 1.73 m^2 body surface) from time of diagnosis (I) to the 3 months investigation (III) in 10 newly diagnosed Type 2 diabetic patients. A significant positive correlation was found: $r = 0.76$, $p = 0.011$

Table 2. Urinary albumin excretion (UAE) and plasma glucose measurements from patients participating in Study B

	No of days	Initial UAE (μg/min)	Last UAE (μg/min)	Initial mean plasma glucose (mmol/l)	Last mean plasma glucose (mmol/l)	*r*	*p*
1	13	73.5	5.8[a]	17.6	4.8	0.81	0.00088
2	8	6.7	6.1[a]	9.7	7.8		NS
3	10	31.2	5.4[a]	16.7	6.8	0.66	0.036
4	13	10.8	3.4[a]	14.4	6.3		NS
5	11	19.1	7.1	12.1	7.8	0.51	(0.107)
6	10	5.4	1.9[a]	14.4	5.1	0.53	(0.117)
7	11	20.3	3.7[a]	17.8	5.2	0.90	0.00013
8	4	21.7	10.8	8.9	8.6		NS
9	15	4.2	6.5[a]	17.5	7.5		NS
10	11	18.3	14.7[a]	12.4	5.7		NS
11	8	2.0	3.0[a]	16.1	7.7		NS
12	10	88.9	46.0[a]	12.4	6.0	0.55	(0.102)
13	4	44.1	2.2	15.2	9.5	0.92	(0.08)
14	7	4.0	4.8[a]	8.3	7.2	0.76	0.048
15	7	8.5	4.4	16.7	9.6		NS

[a] at three month control, mean of two 24 h periods

Discussion

In the present study we found a small but significant ($p<0.05$) reduction in GFR of 9.6% in ten newly diagnosed Type 2 diabetic patients from the untreated state until the time of 3 month's treatment. During the same period mean plasma glucose was near-normalized and body surface decreased. It might be inaccurate to use different correction factors in the same subject over a short period of time, if kidney function does not change due to a moderate loss of weight. This possible source of error, however, would mean that the "true" difference in the corrected GFR values would be slightly greater. The prescribed diet was based on their usual diet and in accordance with the general recommendations: carbohydrate 45–55% (of energy) and a maximum of 35% fat. Thus, protein restriction was not instituted.

The decline in GFR in the present series was moderate compared to the decrease of 20% found in newly diagnosed Type 1 diabetic patients during short-term insulin therapy [1], with comparable initial glucose levels (serum glucose 13.8 ± 1.8 mmol/l). Since the exact time of onset of Type 2 diabetes is almost impossible to assess we chose to investigate otherwise healthy patients without complications (from long-standing undiagnosed diabetes) to avoid a possible reduction in GFR from arteriosclerosis, nephropathy or other diseases. Although unlikely, we cannot exclude the possibility that some patients had initial hyperfiltration before clinical diagnosis. Newly diagnosed patients were chosen to obtain the shortest possible duration of disease as well as poor glycaemic control. In these selected patients using intraindividual comparison it was possible to detect a relative elevation of GFR during poor metabolic control. Comparisons of groups of Type 2 diabetic patients to normal control subjects show no enhancement in GFR [12, 13], in contrast to findings in Type 1 diabetic patients during "ordinary control" [3]. Consequently the characteristic sizeable hyperfiltration of Type 1 diabetes present at diagnosis and lasting for many years [1–4] does not seem to be common in Type 2 diabetes.

KV was decreased in this series, a finding consistent with the reduction in KV seen in short-term Type 1 diabetes [5]. Beta-2-microglobulin is a marker of tubular reabsorptive capacity [22] and simultaneous measurements of urinary excretion rates of albumin and beta-2-microglobulin makes it possible to distinguish between albuminuria caused by increased transglomerular escape or reduced tubular reabsorption. Since the excretion rate of beta-2-microglobulin was unchanged the enhanced albuminuria at diagnosis was caused by an increased glomerular escape. The exact mechanism(s) behind this phenomenon is not elucidated in the present study, and is also unexplained in Type 1 diabetes [23]. It might be caused by an increased filtration pressure [24–26], as also implicated by the correlation between GFR and UAE in the present study and an earlier study on normoalbuminuric Type 2 diabetic patients [13]. In Type 1 diabetes GFR and UAE are associated also for UAE values <30 μg/min [10]. An altered permeability of the glomerular membrane induced by the diabetic state is another possibility [27]. Since, however, glycaemic control, GFR and UAE are covariating it cannot be judged which mechanism is most probable, at least not in a small series.

In study B, UAE was normalized in five of six patients with initial microalbuminuria, and UAE was decreased in twelve of 15 subjects. The three subjects showing a minor increase in UAE all had very low initial values (<5 μg/min) the increase was small and within the expected day to day variation [28]. Normal daily life activities were allowed throughout the study period. It seems unlikely that systematical changes in physical activity, if any, could have had major influence on the results.

Overall, the results from the present investigation indicated a rather strong association between glycaemic control as estimated by the mean of 3 daily plasma glucose values and urinary albumin excretion which is in accordance with earlier studies.

Keen et al. [14] have demonstrated a significant correlation between blood glucose after a glucose load and albumin excretion in predominantly elderly diabetic patients. Mohamed et al. [29] found a reduction in exercise induced albuminuria after dietary treatment in ten newly diagnosed Type 2 diabetic patients, and Vasquez [30] demonstrated that diet induced reduction of hyperglycaemia reduced proteinuria and albuminuria in younger Type 2 diabetic patients. In Vasquez's study no significant correlation was found between changes in glycaemic parameters

(decrease in 2 h plasma glucose level, or fasting plasma glucose) and changes in 24 h albumin excretion, although the initial fasting plasma glucose was correlated weakly ($r = 0.33$) to albumin excretion. In Type 1 diabetes microalbuminuria is also reduced by optimized glycaemic control both in the newly diagnosed patients [7, 8] and in incipient nephropathy [31, 32]. Also during poor control obtained by interruption of insulin therapy UAE was increased in normoalbuminuric patients [33]. On the other hand, infusion or ingestion of glucose has not shown consistent increases in UAE [34, 35]. This might indicate that the causative factor is not glucose per se but some other factor generated by the diabetic state. Alterations in serum lipids and lipoproteins are associated with microalbuminuria and might induce glomerular abnormalities [36], but several biochemical alterations linked to the metabolic derangement may be involved in the glomerular pathology [27].

The increased transglomerular traffic of plasma proteins has been suggested as contributing to the basement membrane thickening and mesangial expansion, characteristic of diabetic glomerulopathy [24]. Basement membrane thickness is already enhanced after few years of disease in Type 1 diabetic patients [37]. The development of glomerular structural lesions in Type 2 diabetes has so far not been described although these patients also develop the classic lesions [38, 39]. On the basis of information from Type 1 diabetes [40] efforts to reduce albuminuria in Type 2 diabetic patients may be worthwhile. The long-term consequences of intervention remain, however, to be elucidated.

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