Diabetologia (1993) 36: 734–740

Diabetologia

Impact of initial treatment on renal function in newly-diagnosed Type 2 (non-insulin-dependent) diabetes mellitus

J. P. Vora[1], J. Dolben[1], J. D. Williams[2], J. R. Peters[1], D. R. Owens[1]

[1] Department of Medicine, University of Wales College of Medicine, Cardiff, UK
[2] Institute of Nephrology, University of Wales College of Medicine, Cardiff, UK

Summary. The impact of improved glycaemic control on renal function in newly-presenting Type 2 (non-insulin-dependent) diabetic patients has not been adequately researched. Consequently, glomerular filtration rate and effective renal plasma flow and urinary albumin excretion rates were determined in 76 subjects (age (mean (SD)): 54 (9.5) years; 50 male) of an original cohort of 110 newly-presenting normotensive non-proteinuric Type 2 diabetic patients following 6 months treatment with diet alone ($n = 42$) or with oral hypoglycaemic agents ($n = 34$). Significant reductions were observed in (presentation vs 6 months): body mass index ($p < 0.01$); fasting plasma glucose ($p < 0.001$); glycated haemoglobin (HbA_1) ($p < 0.001$); systolic blood pressure ($p < 0.01$); and diastolic blood pressure ($p < 0.001$). Glomerular filtration rate declined from 117 (22) to 112 (21) ml · min^{-1} ($p < 0.01$), with unchanged effective renal plasma flow (534 (123) vs 523 (113) ml · min^{-1}) and filtration fraction (22.4 (3.0) vs 21.8 (3.4)%). Albumin excretion rate (median (range)) declined from 1.1 (0.1–34.7) to 0.5 (0.1–29.9) μg · min^{-1} ($p < 0.01$). Changes in glomerular filtration rate (Δ values) were inversely correlated with presentation values ($p < 0.001$), and positive relationships were observed with Δ effective renal plasma flow ($p < 0.01$), and Δ glycated haemoglobin ($p < 0.05$). Type 2 diabetic patients with glomerular filtration rate values at presentation over 120 ml · min^{-1} demonstrated significant reduction in glomerular filtration rate ($n = 31$; $p < 0.001$), whilst those with original values less than 120 ml · min^{-1} remained unchanged ($n = 45$). Glomerular filtration rate, effective renal plasma flow and filtration fraction for the Type 2 diabetic patients remained elevated compared with age-controlled normal subjects ($p < 0.01$–0.001). Albumin excretion rate at presentation and 6 months were positively correlated with fasting plasma glucose levels ($p < 0.05$) but not renal haemodynamics. Thus, glomerular filtration rate and albumin excretion rate in newly-presenting Type 2 diabetic patients are influenced by metabolic control. Improved glycaemia for 6 months produces a reduction in glomerular filtration rate, mainly in the younger patients with values greater than 120 ml · min^{-1} at diagnosis of diabetes. Despite these changes, renal haemodynamic parameters remain elevated compared with age-matched normal subjects.

Key words: Type 2 (non-insulin-dependent) diabetes mellitus, renal haemodynamics, improved glycaemic control.

Early stages of human and experimental insulin-dependent diabetes mellitus are characterized by an elevation of glomerular filtration rate (GFR) [1–6]. In experimental diabetes the single nephron GFR is increased, due to elevations of glomerular capillary plasma flow and pressure, as a consequence of reduction in renal vascular resistance predominantly affecting the afferent arteriole [4–6]. In moderately hyperglycaemic diabetic rats, normalisation of blood glucose levels reverses glomerular hyperfiltration [7]. Institution of insulin therapy in short-term Type 1 (insulin-dependent) diabetic patients results in a reduction in the elevated GFR, though supranormal levels may persist in a proportion of patients [8–10].

Evaluation of renal haemodynamics in Type 2 (non-insulin-dependent) diabetes has yielded conflicting results [11–15]. Some workers failed to demonstrate glomerular hyperfunction in Type 2 diabetic patients [11, 12]. Others have reported elevations in GFR in significant proportions of Type 2 diabetic patients of Caucasian, Native- and Afro-American origin [13–15]. In 110 newly-presenting normotensive non-proteinuric Type 2 diabetic patients, we have observed a wide range of renal haemodynamics with higher GFR, effective renal plasma flow (ERPF) and filtration fraction (FF) compared with normal subjects of similar age range evaluated for comparative purposes [13]. Hyperfiltration, as defined by GFR values above mean + 2 SD for the normal subjects

($120\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), was detected in 45% of this patient population. As part of an on-going longitudinal study, this report examines the effect on renal function of initial treatment for Type 2 diabetes in our original cohort of patients.

Subjects and methods

Determination of renal haemodynamics and metabolic parameters was performed in a group of 110 consecutive newly-presenting previously untreated, islet-cell antibody-negative Caucasian Type 2 diabetic patients, who were receiving no concomitant medication [13]. Diagnosis of Type 2 diabetes at presentation was made on clinical basis, absence of ketonuria and biochemical classification by the World Health Organisation (WHO) criteria [16]. All patients selected were normotensive, according to the WHO criteria [17]. Patients with possible pre-existing renal disease, as suggested by an increased serum creatinine level (above 120 μmol/l), haematuria or proteinuria were excluded from the study. Subsequently, all patients embarked on dietary treatment for Type 2 diabetes for a 3-month period. The proposed dietary composition was 50–55% carbohydrate, 30–35% fat and 15% protein [18]. Persistent hyperglycaemia (fasting plasma glucose in excess of 9.0 mmol/l or glycated haemoglobin (HbA_1) level above 9%) at this stage resulted in the introduction of oral hypoglycaemic agents, in addition to continuing dietary advice, for a further period of 3 months. During this initial 6-month treatment period, patients were reviewed at frequent intervals as indicated on clinical grounds. Modification in treatment was based on clinical and biochemical response. Full informed written consent was obtained from all patients. The study was approved by the local area Health Authority Ethics Committee and performed in accordance with the principles of the Declaration of Helsinki.

Of the original cohort of 110 patients, 76 (mean(SD) age: 54.5 (9.5) years; 50 male) attended for re-evaluation of renal haemodynamics and metabolic parameters following the 6-month treatment period. Of the remaining 34 patients, 29 declined to participate for personal reasons, one died of unknown cause, one suffered a cerebrovascular accident, one underwent coronary artery by-pass grafting, and two required insulin therapy for poor metabolic control despite maximal doses of oral hypoglycaemic agents. Renal haemodynamics, metabolic parameters and blood pressure were determined as previously described [13, 19]. Briefly, GFR and ERPF were determined following an overnight fast. Fasting blood samples were obtained for measurement of plasma glucose, lipid and HbA_1 levels. Thereafter, subjects were administered a single i.v. injection containing 1 mBq each of ^{51}Cr-EDTA and ^{125}I-iodohippurate (Amersham International, Amersham, Bucks, UK) for the simultaneous determination of GFR and ERPF [13, 19]. Following the administration of the radiotracers, blood samples were obtained from the contralateral arm at 44 min, 2, 3 and 4 h. Subjects remained supine for the entire 4-h study period and smoking was not permitted. Supine systolic and diastolic (phase V) blood pressures were measured to the nearest 2 mm Hg during the clearance procedure, using an appropriate 15 × 33 cm cuff for obese patients. Body mass index (BMI) was calculated as weight/[height^2], measured with subjects wearing indoor clothing.

GFR and ERPF were determined from the plasma clearance of the respective radioisotope and corrected to 1.73 m^2 surface area [13, 19]. FF was calculated as the ratio of GFR to ERPF. Following careful instruction, patients provided a timed overnight urine collection at diagnosis and 6 months for the measurement of albumin excretion rate (AER) using a sensitive immunochemiluminescence technique [20]. Plasma glucose levels were determined by a glucose oxidase method [21]. Total cholesterol and triglyceride levels were measured using enzymatic techniques on the Technicon RA 1000 analyser (Technicon Instruments Co. Ltd., Basingstoke, Hants., UK) [22, 23]. Measurement of HDL-cholesterol was performed using the same technique, following heparin manganese precipitation of VLDL- and LDL-cholesterol [24]. LDL-cholesterol was calculated using the Friedewald formula [25]. HbA_1 was determined chromatographically (reference range 5.5–8.0%) [26].

Statistical methods

Analyses of the results were performed using the Minitab Release 8 statistical package [27]. Comparisons between renal haemodynamics, metabolic parameters and blood pressure at presentation and 6 months were performed using Student's t and Wilcoxon tests for paired data, as appropriate. The Mann-Whitney U test was utilised to compare the 6-month data for the Type 2 diabetic patients, with renal haemodynamics in a group of normal subjects of similar age range ($n = 32$; mean (SD) age: 52.2 (11.3) years) [13]. AER were transformed (logarithmic to base 10) prior to examination of relationships with renal and metabolic parameters. Linear regression analyses were performed to assess bivariate relationships. Thereafter, modelling of several variables simultaneously was performed by means of multiple stepwise regression analyses, using appropriate models. Significances of regression analyses were assessed by analysis of variance. Relative contributions of different independent on dependent variables were evaluated by analysis of covariance. Statistical significance was set as p values below 0.05. Results are expressed as mean (SD), unless otherwise stated, with appropriate ranges in parentheses.

Results

Clinical and biochemical data for the Type 2 diabetic patients at presentation and following the initial 6-month treatment period are summarised in Table 1. During this 6-month period, 42 patients required dietary treatment alone, whilst additional oral hypoglycaemic therapy was necessary for the remaining 34. Paired comparisons re-

Table 1. Mean (SD) clinical and biochemical parameters in Type 2 diabetic patients, at presentation and following therapy for 6 months

	Presentation	6 months
Age (years)	52.5 (10.1)	
Body mass index (kg/m^2)	28.7 (5.1)	27.5 (4.5)[a]
Blood pressure (systolic) (mm Hg)	131 (17)	127 (16)[a]
Blood pressure (diastolic) (mm Hg)	82 (9)	78 (10)[b]
Fasting plasma glucose (mmol/l)	12.4 (3.3)	8.7 (2.3)[b]
Glycated haemoglobin (%)	11.2 (2.3)	8.6 (1.3)[b]
Total cholesterol (mmol/l)	5.6 (1.4)	5.4 (1.3)
HDL-cholesterol (mmol/l)	1.1 (0.9)	1.0 (0.4)
LDL-cholesterol (mmol/l)	3.4 (1.1)	3.6 (1.1)
Triglycerides (mmol/l)	2.3 (1.1)	2.0 (1.0)

[a] $p < 0.01$, [b] $p < 0.001$ vs presentation

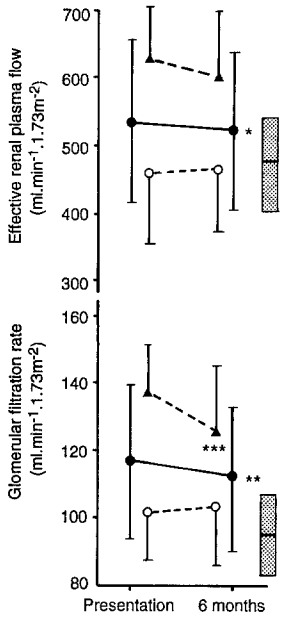

Fig. 1. Mean (± SD) glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in Type 2 diabetic patients at presentation and following 6 months' therapy. Δ and ○ represent subsets of the Type 2 patients, according to GFR above or below 120 ml · min^{-1} · 1.73 m^{-2} at presentation. ▨ mean (± SD) GFR and ERPF for age-controlled normal subjects. * – NS, ** $p < 0.01$, *** $p < 0.001$ presentation vs 6 months

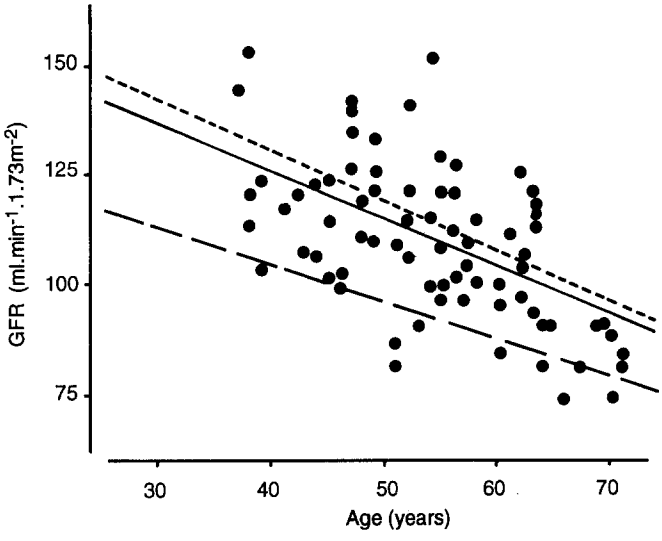

Fig. 2. Relationship between glomerular filtration rate and age for Type 2 diabetic patients after 6 months therapy (—). Similar relationships shown for Type 2 diabetic patients at presentation (- - -) and normal subjects (– – –)

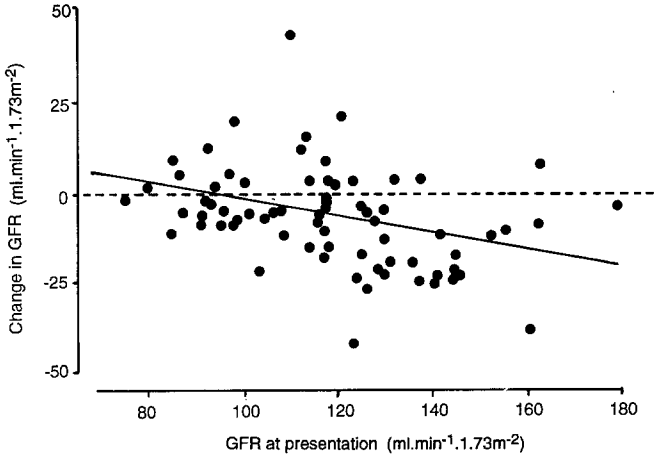

Fig. 3. Relationship between change in glomerular filtration rate (GFR) during the initial 6-month treatment period with GFR at presentation of Type 2 diabetes

vealed significant reductions in BMI ($p < 0.01$), fasting plasma glucose (FPG) ($p < 0.001$) and HbA_1 levels ($p < 0.001$), systolic ($p < 0.01$) and diastolic blood pressures ($p < 0.001$) (Table 1). Changes in total cholesterol, HDL- and LDL-cholesterol and triglyceride levels did not achieve statistical significance.

GFR and ERPF at 6 months were 112 (20) (range: 75–176) ml · min^{-1} and 523 (114) (range: 278–794) ml · min^{-1}. GFR was reduced from 117 (22) (range: 74–178) ml · min^{-1} at presentation ($p < 0.01$); ERPF was unchanged from 534 (123) (range: 258–821) ml · min^{-1} (Fig. 1). FF at presentation and 6 months of 22.4 (3.0) and 21.8 (3.4)% were not significantly different. In terms of the achieved glycaemic level, GFR values were similar for patients with HbA_1 values below ($n = 52$) and above 9% ($n = 24$), at 107 (16) and 112 (20) ml · min^{-1}, respectively. However, ERPF was higher for Type 2 diabetic patients with HbA_1 less than 9% at 536 (101) ml · min^{-1} compared with 477 (116) ml · min^{-1}, for those with HbA_1 levels above 9% ($p < 0.05$), and consequently FF of 21.2 (3.3) was lower for the former than 23.1 (3.7)% for the latter group of patients ($p < 0.05$). Conversely, HbA_1 values at 6 months were similar for patients with GFR values greater than ($n = 25$) or below 120 ml · min^{-1} ($n = 51$), at 8.4 (1.1) and 8.6 (1.4)%, respectively. Likewise, GFR values at 6 months were similar for patients requiring dietary therapy alone or in conjunction with oral hypoglycaemic agents, at 114 (24) and 109 (14) ml · min^{-1}, respectively.

GFR at 6 months demonstrated a significant positive relationship with ERPF ($p < 0.001$), and an inverse association with age (GFR = 168 – 1.07 age: $R^2 = 31\%$; $p < 0.001$) (Fig. 2). Similarly, ERPF declined with age ($p < 0.001$). Significant relationships were not observed for either GFR, ERPF or FF with BMI, parameters of glycaemic control, lipid levels nor systolic or diastolic blood pressures. Multivariate analyses with GFR as the dependent variable revealed a regression equation of GFR = 94 – 0.57 age + 0.09 ERPF: $R^2 = 52\%$; $p < 0.001$).

Significant bivariate relationships for the changes in GFR (Δ values) were noted with GFR at presentation (Δ GFR = 21 – 0.23 GFR at presentation: $R^2 = 13\%$; $p < 0.001$) (Fig. 3), Δ ERPF (Δ GFR = –5 + 0.07 Δ ERPF: $R^2 = 10\%$; $p < 0.01$) and Δ HbA_1 (Δ GFR = –1.5 + 1.69 Δ HbA_1: $R^2 = 4\%$; $p < 0.05$) (Fig. 4). The resulting multivariate regression equation was Δ GFR = 25 – 0.24 presentation GFR + 0.05 Δ ERPF + 1.16 Δ HbA_1 ($R^2 = 28\%$; $p < 0.001$). Significant contributions to Δ GFR were not noted for alterations in BMI, lipid parameters or systolic and diastolic blood pressures. The reduction in GFR during this 6-month treatment period did not significantly alter its relationship with either ERPF or age, compared with at presentation. Thus, the differences in the slopes for regression analysis between GFR and ERPF of –0.02 (95% confidence interval (CI): –0.05 to 0.01) and for GFR with age of 0.76 ml · min^{-1} · 10 years^{-1} (95% CI: –0.43 to 0.58) (Fig. 2) were not significant. Likewise, the relationship for ERPF with age was similar at 0 and 6 months (difference in slopes: 1.60 ml · min^{-1} · 10 years^{-1} (95% CI: –28.4 to 31.5).

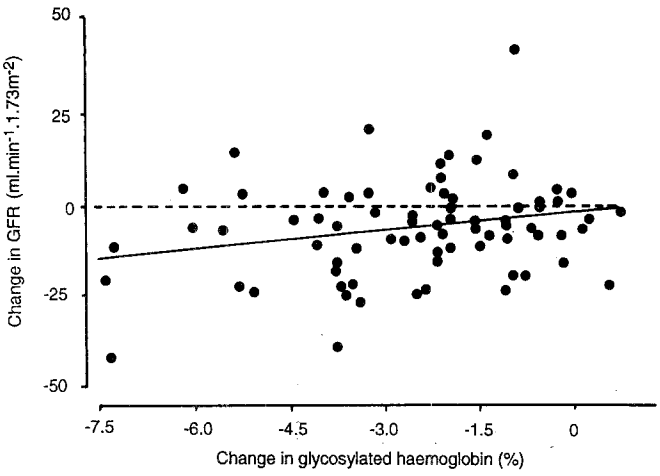

Fig. 4. Relationship between changes in glomerular filtration rate and glycosylated haemoglobin levels during the initial 6-month treatment period following the diagnosis of Type 2 diabetes

Table 2. Mean (SD) clinical, biochemical and renal parameters for the Type 2 diabetic patients at presentation and following 6 months' treatment. Results are sub-divided according to glomerular filtration rate (GFR) below or above 120 ml · min^{-1} · 1.73m^{-2} at diagnosis

	Presentation		6 months	
Glomerular filtration rate at presentation (ml · min^{-1})	< 120	> 120	< 120	> 120
Age (years)	55.8 (10.1)	48.7 (8.7)[a]		
Body mass index (kg/m^2)	28.3 (5.0)	29.4 (5.3)	27.1 (5.0)[d]	28.2 (3.6)[c]
Fasting plasma glucose (mmol/l)	12.3 (3.6)	12.4 (3.0)	8.9 (2.6)[d]	8.3 (1.3)[d]
Glycated haemoglobin (%)	11.1 (2.3)	11.3 (2.3)	8.7 (1.5)[d]	8.3 (0.8)[d]
Blood pressure (systolic) (mm Hg)	132 (17)	128 (16)	128 (17)[b]	124 (15)[b]
Blood pressure (diastolic) (mm Hg)	82 (9)	82 (8)	78 (10)[b]	78 (10)[c]
Glomerular filtration rate (ml · min^{-1})	102 (16)	137 (14)[a]	103 (16)	125 (20)[a,d]
Effective renal plasma flow (ml · min^{-1})	461 (101)	624 (81)[a]	466 (93)	601 (93)[a]

[a] $p < 0.001$ between sub-groups; [b] $p < 0.05$, [c] $p < 0.01$, [d] $p < 0.001$ within sub-groups

Comparison of the Type 2 diabetic patients' renal haemodynamics following 6 months therapy with an age-matched group of normal subjects [13], revealed significantly greater GFR ($p < 0.001$), ERPF ($p < 0.01$) and FF ($p < 0.01$) than respective values of 95 (12) ml · min^{-1}, 472 (70) ml · min^{-1} and 20.2 (2.2)% for the normal subjects (Fig. 1). At 6 months, 25 (32%) and 7 (9%) of the Type 2 diabetic patients demonstrated GFR values above 120 and 140 ml · min^{-1}, respectively. The relationships for GFR with ERPF, GFR with age and ERPF with age were similar for the Type 2 patients at 6 months and the normal subjects, with respective differences in the slopes of the regression analyses of 0.01 (95% CI: −0.04 – 0.06), −2.5 ml · min^{-1} · 10 years^{-1} (95% CI: −6.9–1.9) and −26.5 ml · min^{-1} · 10 years^{-1} (95% CI: −56.5–3.1). In keeping with the higher FF for the Type 2 diabetic patients compared with the normal subjects, analysis of covariance demonstrated an elevation of GFR in the patients of 11 (3) ml · min^{-1} above that explained by the raised ERPF. As at presentation, BMI, metabolic parameters and blood pressure were without significant effect on the observed differences in renal haemodynamics between the Type 2 diabetic patients and normal subjects.

In light of the above relationship of Δ GFR with GFR values at presentation and the persistent differences between the Type 2 diabetic patients and normal subjects, sub-group analyses were conducted for the patients with GFR values at presentation of diabetes greater than or below 120 ml · min^{-1} (corresponds to mean + 2 SD for the normal subjects). Despite comparable alterations in BMI, parameters of glycaemic control and lipid levels (Table 2), significant reduction in GFR was observed in those patients with GFR at presentation above 120 ml · min^{-1} ($n = 31$) (137 (14) to 125 (20) ml · min^{-1}; $p < 0.001$) but not for those with original GFRs below 120 ml · min^{-1} ($n = 45$) (102 (14) to 103 (16) ml · min^{-1}) (Fig. 1). ERPF values were unchanged for both groups, from 624 (81) to 601 (93) ml · min^{-1} (GFR > 120 ml · min^{-1}) and 461 (101) to 466 (93) ml · min^{-1} (GFR < 120 ml · min^{-1}). Consequently, FF decreased from 22.1 (2.5) to 21.0 (2.7)% for Type 2 diabetic patients with GFRs greater than 120 ml · min^{-1} ($p < 0.05$), but remained unaltered for the other sub-group, from 22.6 (3.4) to 22.5 (3.7)%. Comparisons between these two sub-groups revealed patients with GFR greater than 120 ml · min^{-1} to be younger at diagnosis of diabetes, with mean age of 48.7 (8.7) years compared with 55.8 (10.1) years for those with GFR less than 120 ml · min^{-1} ($p < 0.001$). Significant differences were not observed between the two groups for glycaemic control, lipid parameters or blood pressure levels at presentation or 6 months.

Median AER at presentation was 1.0 μg · min^{-1} (range: 0.1–35.0), with 6.6% of the patients demonstrating AER above 20 μg · min^{-1}. Following logarithmic transformation, AER for the Type 2 diabetic patients was associated with FPG (log AER = −1.3 + 0.12 FPG: $R^2 = 5\%$; $p = 0.036$). Median AER at 6 months was reduced to 0.5 μg · min^{-1} (range: 0.01–30) ($p < 0.01$), with only one subject demonstrating AER above 20 μg · min^{-1}. AER at 6 months was significantly related to AER at presentation and FPG (log AER (6 months) = −3.9 + 0.38 log AER (presentation) + 0.34 FPG: $R^2 = 28\%$; $p < 0.001$). Significant relationships were not observed for AER at presentation or 6 months with GFR, ERPF, FF, systolic and diastolic blood pressure, or lipid levels.

Discussion

Improved glycaemic control during the initial 6 months of treatment for newly-presenting non-proteinuric normotensive Type 2 diabetic patients results in a significant re-

duction in GFR. The changes in GFR were related to reduction in glycaemic levels and ERPF, as manifest by a positive relationship for Δ GFR with Δ $HbA_1$and Δ ERPF, respectively. A significant association for changes in GFR and ERPF was noted despite significant reduction only in the former parameter. The observed reduction in GFR for this group of patients, though smaller than those reported following commencement of insulin therapy in Type 1 diabetic patients [8–10], was evident despite their comparatively advanced age and an estimated 4–7-year period of sub-clinical hyperglycaemia prior to the clinical diagnosis of Type 2 diabetes [28].

The influence on renal haemodynamics of improved glycaemic control following the diagnosis of Type 2 diabetes has not been adequately researched. In a study of 10 patients, GFR declined from 106 (15) at presentation to 96 (14) $ml \cdot min^{-1}$ following 3 months' treatment with diet alone or additional oral hypoglycaemic agents [29]. A reduction in GFR with the institution of treatment for Type 2 diabetes was similarly observed in our study. GFR values at presentation and 6 months were not correlated with fasting plasma glucose or HbA_1 levels, and GFRs were similar for patients with HbA_1 levels above or below 9%. However, the reduction in GFR during this period demonstrated a significant association with Δ HbA_1. Further, the strongest association for Δ GFR was the GFR values at presentation. Consequently, a significant reduction in GFR was noted for the younger Type 2 diabetic patients with GFRs greater than 120 $ml \cdot min^{-1}$ at diagnosis but not for the older patients with GFRs below this value. As ERPF levels were unchanged in either sub-group during this treatment period, a significant reduction in FF was noted for those patients with presentation GFRs above 120 $ml \cdot min^{-1}$. The different response in renal haemodynamics for the two sub-groups, despite similar alterations in demographic and biochemical parameters, may reflect a pre-existing state of relative renal vascular vasodilatation in a less compliant vasculature with advancing age [30]. One may also speculate a longer duration of subclinical hyperglycaemia prior to the diagnosis of Type 2 diabetes in the older patients with GFR values above 120 $ml \cdot min^{-1}$.

GFR, ERPF and FF for the Type 2 diabetic patients following 6 months' therapy remain significantly elevated compared with age-controlled normal subjects [13]. GFR values above 120 $ml \cdot min^{-1}$ (mean + 2 SD for age-controlled normal subjects) were noted in 32% of the patients compared with 45% at presentation of Type 2 diabetes. Thus, a significant proportion of the Type 2 diabetic patients demonstrate persistent hyperfiltration despite improved glycaemic control. However, this study and our previous findings provide only limited insights into the pathophysiology of the elevation of GFR in Type 2 diabetes. Of the determinants of GFR, the raised ERPF for the Type 2 diabetic patients, with the attendant strong relationship between GFR and ERPF, suggests a significant contribution of the raised plasma flow to the observed elevation of GFR. The higher FF in the Type 2 diabetic patients and the demonstration by analysis of covariance of an increase in the GFR over that explicable by the raised ERPF, suggests an elevation of transcapillary hydraulic pressure alone or in combination with a raised ultrafiltration coefficient. Consistent with this notion would be the recent finding of a positive correlation between glomerular capillary surface area and GFR in morphometric analysis of renal biopsy material from a heterogeneous group of Type 2 diabetic patients [31], as previously established for Type 1 diabetic patients [32].

Considerable experimental evidence exists implicating the deranged renal haemodynamics of early diabetes, specifically glomerular capillary hypertension, in the later development of glomerulopathy [33–36]. It has also been proposed that the glomerular hyperfunction of early Type 1 diabetes predicts the development of nephropathy [37, 38], a hypothesis not uniformly accepted [39, 40]. The role of the hyperfiltration observed in a significant portion of our group of Type 2 diabetic patients in the subsequent development of nephropathy remains to be established in our on-going longitudinal study. Since evaluation of renal haemodynamics in this study was performed in the fasted state, the observed hyperfiltration would be amplified by the augmentation of GFR in response to meal ingestion [41, 42].

The prevalence of microalbuminuria, using AER of 20–200 $\mu g \cdot min^{-1}$ [43], in our preselected normotensive Type 2 diabetic patients was 7% at the time of presentation, lower than previously reported for cohorts of newly-diagnosed patients [44–46]. However, these previous studies have variously included patients with other concomitant conditions and therapies, such as hypertension, which may alter albumin excretion. In the absence of such concomitant conditions, the prevalence of microalbuminuria in newly-presenting Type 2 diabetic patients may be lower than previously reported, though direct comparisons between such studies are hindered by the different urine collections and assay techniques used. At diagnosis and 6 months, AER was correlated with fasting plasma glucose levels but not with renal haemodynamics, blood pressure or lipid parameters. Institution of therapy for Type 2 diabetes resulted in a significant decline in AER. At 6 months AER was also related to AER at presentation. No association was observed for change in AER with alteration in renal haemodynamics or blood pressure.

AER at diagnosis of Type 2 diabetes and subsequent reductions during treatment have been reported to correlate with the prevailing level of glycaemic control [29, 44, 45]. Short-term reductions in AER also correlated with Δ GFR [29]. Although the influence of glycaemic control on AER at diagnosis and at 6 months was confirmed by our findings, AER was not correlated with renal haemodynamics. This disparity may reflect the considerably wider ranges of GFR and its response during therapy observed in our study. The enhanced albumin excretion at diagnosis of Type 2 diabetes may be attributed to increased glomerular filtration, due to raised filtration pressure or a direct alteration of barrier size selectivity [15, 29]. The latter abnormality, recently demonstrated in Pima Indians with Type 2 diabetes of short duration [15], supports our finding of a lack of a direct relationship between changes in AER and renal haemodynamics.

In summary, improved glycaemic control following the diagnosis of Type 2 diabetes produces a reduction in GFR, mainly in younger patients with GFR values above 120 ml · min^{-1}. However, hyperfiltration persists in a significant proportion of the patients, and its long-term effects on renal function in Type 2 diabetes remain to be established in our on-going longitudinal study.

Acknowledgements. This study is supported in part by a British Diabetic Association Project Grant. We acknowledge the assistance of Ms H. Smith and Ms S. Porter in conducting the study. Statistical analyses were performed under the guidance of Dr. R. Newcombe, Department of Medical Computing and Statistics. We are grateful to Dr. S. Anderson for critical review of the manuscript. Presented in part at the Annual Meeting of the American Diabetes Association, June 1992.

References

1. Stadler G, Schmidt R (1959) Severe functional disorders of glomerular capillaries and renal hemodynamics in treated diabetes mellitus during childhood. Ann Paediatr 193: 129–138
2. Ditzel J, Junker K (1972) Abnormal glomerular filtration rate, renal plasma flow and renal protein excretion in recent and short-term diabetes. BMJ 2: 13–19
3. Mogensen CE (1972) Glomerular filtration rate and renal plasma flow in short-term and long-term juvenile diabetes mellitus. Scand J Clin Lab Invest 28: 91–100
4. Hostetter TH, Troy JL, Brenner BM (1981) Glomerular hemodynamics in experimental diabetes. Kidney Int 19: 410–415
5. Zatz R, Meyer TW, Anderson S, Rennke HG, Brenner BM (1985) Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. Proc Natl Acad Sci USA 82: 5963–5967
6. Hostetter TH (1992) Diabetic nephropathy: metabolic versus hemodynamic considerations. Diabetes Care 15: 1205–1215
7. Stackhouse S, Miller PL, Park SK, Meyer TW (1990) Reversal of glomerular hyperfiltration and renal hypertrophy by blood glucose normalization in diabetic rats. Diabetes 39: 989–995
8. Christensen JS, Frandsen M, Parving H-H (1981) The effect of intravenous insulin infusion on kidney function in insulin-dependent diabetes mellitus. Diabetologia 20: 199–204
9. Mogensen CE, Andersen MJF (1975) Increased kidney size and glomerular filtration rate in untreated juvenile diabetics: normalization by insulin treatment. Diabetologia 11: 221–224
10. Mogensen CE (1972) Kidney function and permeability to macromolecules in juvenile diabetes. Dan Med Bull 19: 1–40
11. Schmitz A, Christensen T, Taagehoej Jensen F (1989) Glomerular filtration rate and kidney volume in normoalbuminuric non-insulin-dependent diabetics – lack of glomerular hyperfiltration and renal hypertrophy in uncomplicated NIDDM. Scand J Clin Lab Invest 49: 103–108
12. Friedman EA (1988) No supranormal GFR in type II diabetics. Kidney Int 31: 179 (Abstract)
13. Vora J, Dolben J, Dean J et al. (1992) Renal haemodynamics in newly presenting non-insulin-dependent diabetics. Kidney Int 41: 829–835
14. Palmisano JJ, Lebovitz HE (1989) Renal function in Black Americans with type II diabetes. J Diab Compl 3: 40–44
15. Myers BD, Nelson RG, Williams GW et al. (1991) Glomerular function in Pima Indians with non-insulin-dependent diabetes mellitus of recent origin. J Clin Invest 88: 524–530
16. World Health Organisation Expert Committee (1980) Second report on Diabetes Mellitus. Technical Report series No. 646. WHO, Geneva
17. World Health Organisation Expert Committee (1978) Arterial hypertension. Technical Report series No 628. WHO, Geneva
18. Alberti KGMM, Gries FA (1988) Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. Diabetic Med 5: 275–281
19. Vora JP, Burch A, Owens DR, Peters JR (1991) Simultaneous determination of glomerular filtration rate and effective renal plasma flow. Clin Physics Physiol Measurement 12: 269–277
20. Horton JK, Davies M, Woodhead JS, Weeks I (1989) A rapid and sensitive method for estimating low concentrations of albumin in human urine. Clin Chim Acta 186: 45–52
21. Trinder P (1969) Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem 6: 24–27
22. Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC (1974) Enzymatic determination of total serum cholesterol. Clin Chem 20: 470–475
23. Fossati P, Prencipe L (1982) Serum triglycerides determined calorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem 28: 2077–2080
24. Burnstein M, Scholnick HR, Morphin R (1970) Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res 11: 583–595
25. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of preparative ultracentrifuge. Clin Chem 18: 499–502
26. Schnek AG, Schroeder WA (1961) The relation between the minor components of whole normal adult hemoglobin as isolated by chromatography and starch block electrophoresis. J Am Chem Soc 83: 1472–1476
27. Minitab Reference Manual – Release 8 (1991) Minitab Inc., State College, PA, USA
28. Harris MI, Klein R, Welborn TA, Knuiman MW (1992) Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. Diabetes Care 15: 815–819
29. Schmitz A, Hvid Hansen H, Christensen T (1989) Kidney function in newly diagnosed type 2 (non-insulin-dependent) diabetic patients, before and during treatment. Diabetologia 32: 434–439
30. Hollenberg NK, Adams DF, Solomon HS, Rashid A, Abrams HL, Merrill JP (1974) Senescence and the renal vasculature in normal man. Circ Res 34: 309–316
31. Hayashi H, Karasawa R, Inn H et al. (1992) An electron microscopic study of glomeruli in Japanese patients with non-insulin-dependent diabetes mellitus. Kidney Int 41: 749–757
32. Ellis EN, Steffes MW, Chavers B, Mauer SM (1986) Glomerular filtration surface in type 1 diabetes mellitus. Kidney Int 29: 889–894
33. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM (1986) Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. J Clin Invest 77: 1925–1930
34. Meyer TW, Anderson S, Rennke HG, Brenner BM (1987) Reversing glomerular hypertension stabilizes established glomerular injury. Kidney Int 31: 752–759
35. Anderson S, Rennke HG, Garcia DL, Brenner BM (1989) Short and long term effects of antihypertensive therapy in the diabetic rat. Kidney Int 36: 526–536
36. Fujihara CK, Padilha RM, Zatz R (1992) Glomerular abnormalities in long-term experimental diabetes. Diabetes 41: 286–293
37. Mogensen CE (1986) Early glomerular hyperfiltration in insulin-dependent diabetics and late nephropathy. Scand J Clin Lab Invest 46: 201–206
38. Rudberg S, Persson B, Dahlquist G (1992) Increased glomerular filtration rate as a predictor of diabetic nephropathy – an 8 year prospective study. Kidney Int 41: 822–828
39. Lervang H-H, Jensen S, Borchner-Mortensen J, Ditzel J (1988) Early glomerular hyperfiltration and the development of late nephropathy in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 31: 723–729
40. Messent J, Jones SL, Wiseman M, Viberti GC (1991) Glomerular hyperfiltration and albuminuria: an 8 year prospective study. Diabetologia 34 [Suppl 2]: A3 (Abstract)

41. Tuttle KR, Bruton JL (1992) Effect of insulin therapy on renal haemodynamic response to amino acids and renal hypertrophy in non-insulin-dependent diabetes. Kidney Int 42: 167–173
42. Vora JP, Thomas D, Williams J, Coles G, Peters JR (1991) Non-insulin dependent diabetics (NIDDMs) and normal subjects demonstrate similar renal haemodynamic responses to oral protein load. Diabetes 40 [Suppl 1]: A438 (Abstract)
43. Mogensen CE, Chachati A, Christensen CK et al. (1986) Microalbuminuria: an early marker of renal involvement in diabetes. Uraemia Invest 9: 85–89
44. Patrick AW, Leslie PJ, Clarke BF, Frier BM (1990) The natural history and associations of microalbuminuria in type 2 diabetes during the first year after diagnosis. Diabetic Med 7: 902–908
45. Damsgaard EM, Mogensen CE (1986) Microalbuminuria in elderly hyperglycaemic patients and controls. Diabetic Med 3: 430–435
46. Uusitupa M, Siitonen O, Penttila I, Aro A, Pyorala K (1978) Proteinuria in newly diagnosed type II diabetic patients. Diabetes Care 10: 191–194

Received: 17 December 1992
and in revised form: 17 March 1993

Dr. J. P. Vora
Division of Nephrology, PP262
Oregon Health Sciences University
3181 SW Sam Jackson Park Road
Portland, OR 97201
USA