Hyperfiltration in African-American Patients With Type 2 Diabetes

Cross-sectional and longitudinal data

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OBJECTIVE — Hyperfiltration may play a role in the development of diabetic nephropathy. African-American patients with diabetes have more than a fourfold increase in end-stage renal disease. The purpose of this study is to evaluate the impact of hyperfiltration on renal function in African-American patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Renal function of 194 African-American patients with diagnosed type 2 diabetes from 1 month to 36 years was assessed by studies of isotopic glomerular filtration rate (GFR), serum creatinine, creatinine clearance, and 24-h urinary albumin excretion rates. Thirty-four patients with a duration of diagnosed type 2 diabetes from 1 month to 10 years were found to have hyperfiltration (GFR $\geq$140 ml · min^{-1} · 1.73 m^{-2}). Fifteen of these patients received longitudinal follow-up of renal function for as long as 15 years after the initial study.

RESULTS — Hyperfiltration is present in 15 (36%) of 42 patients whose duration of diagnosed type 2 diabetes is <1 year, and it persists for up to 10 years in 14–20% of patients with diagnosed type 2 diabetes. Patients with hyperfiltration are younger than their counterparts without hyperfiltration when matched for duration of diagnosed diabetes. When followed over time, those patients with hyperfiltration were not more likely to develop impaired renal function as measured by GFR or creatinine clearance.

CONCLUSIONS — Hyperfiltration does not identify patients at risk for deterioration in renal function.

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Hyperfiltration has been postulated to be an important factor in the development of nephropathy associated with diabetes, particularly type 1 diabetes (1–5). Mogensen et al. (6) have divided the development of diabetic renal changes into stages. The first stage, which can last as long as 10 years after diagnosis, is characterized by hyperfiltration. Microalbuminuria then develops, although hyperfiltration persists. As microalbuminuria progresses to clinical proteinuria, the glomerular filtration rate (GFR) falls, and hypertension develops. This process terminates in end-stage renal disease (ESRD).

ESRD occurs in 25–35% of patients with type 1 diabetes (7). In type 2 diabetes, the rates of ESRD vary according to the population studied. ESRD occurs in 15–20% of African-American type 2 diabetic patients, and this rate is 4.3-fold higher than that in white type 2 diabetic patients (8).

Previously, we reported the presence of hyperfiltration in 15 of 72 African-American type 2 diabetic patients with a duration of disease ranging from <1 to >15 years (9). Seven of these had diagnosed diabetes for <1 year. We expanded our cross-sectional study and presented the renal function in 194 African-American patients with type 2 diabetes (10). This study characterizes the 34 subjects with hyperfiltration and provides longitudinal data of renal function in 15 subjects with a duration of diagnosed diabetes up to 18 years.

RESEARCH DESIGN AND METHODS

Study subjects

All patients who were referred to the diabetes and endocrine clinics at State University of New York–Health Science Center (SUNY-HSC) University Hospital and the affiliated Kings County Hospital Center from 1986 to 1995 were asked to participate in the study, and baseline renal function was collected in 194 African-American patients. Patients had type 2 diabetes as defined by the National Diabetes Data Group (11). The duration of diagnosed type 2 diabetes ranged from 1 month to 36 years. The study protocol was approved by the Institutional Review Board at SUNY-HSC at Brooklyn. Subjects were enrolled after signing informed consent forms. Subjects were studied after an overnight fast at the Clinical Research Center. Medication for diabetes, if required, was not given during the morning of the study. Subjects were considered to be hypertensive for the analyses if they had a history of hypertension and were on medication, or if their blood pressure on several readings was $\geq$140 mmHg systolic and $\geq$90 mmHg diastolic, or if their mean arterial pressure was $\geq$106.

Methods

GFR, the plasma volume filtered by the kidney glomeruli per minute, and effective

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J.P. is currently employed by Merck, but was not at the time of this study.

Abbreviations: AER, albumin excretion rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RPF, renal plasma flow; SUNY-HSC, State University of New York–Health Science Center.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

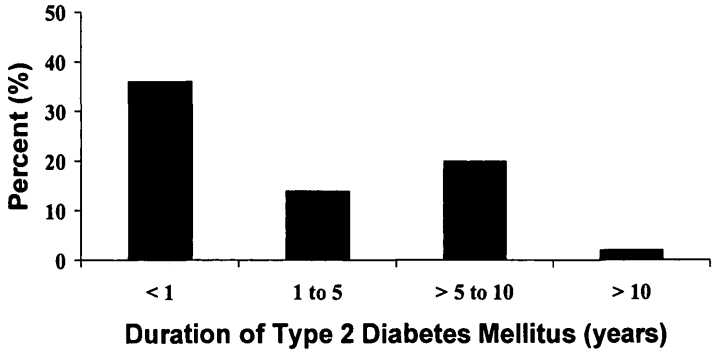

Figure 1—*The percentage of African-American type 2 diabetic patients with hyperfiltration presented according to duration of diagnosed diabetes: 36% (15 of 42) at <1 year, 14% (8 of 57) at 1–5 years, 20% (10 of 50) at >5–10 years, and 2% (1 of 45) at >10 years.*

renal plasma flow (RPF), the plasma volume perfusing the entire kidney per minute, were measured in recumbent subjects by a constant infusion technique with ^{125}I-labeled iothalamate and ^{131}I-labeled hippuran (Iso-Tex, Friendswood, TX) (12). Details of the study protocol were described previously (10). GFR and RPF were calculated from the standard clearance formulas. GFR and RPF values were the means of the values for the four periods and had been corrected to 1.73 m^2 of body surface area. Hyperfiltration is defined as GFR ≥140 ml · min^{-1} · 1.73 m^{-2}, which is >2 SD of the GFR of our normal control subjects.

In the longitudinal analysis, if isotopic GFRs could not be obtained, GFR was determined by 24-h urine collection for creatinine clearance corrected to 1.73 m^2 (13).

Glycohemoglobin was measured by either high-performance liquid chromatography, column chromatography separation technique (SmithKline Beecham, Los Angeles, CA), or DCA 2000 (Miles, Elkhart, IN). Because of the different methods used, all values were expressed as the percentage of the upper limit of the normal value for the given method. Plasma glucose was measured by the glucose oxidase method using a Beckman glucose analyzer.

Urinary albumin measurements were assayed in 24-h urine collections using the Albumin Double Antibody Kit (Diagnostic, Los Angeles, CA).

Statistical analyses

Statistical analyses of the difference of the means were determined by the two-sample (two-tailed) Student's *t* test and by multivariate analyses where indicated (14). Data are presented as means ± SEM.

RESULTS — Figure 1 shows the number of patients with hyperfiltration according to duration of type 2 diabetes. With <1 year's duration of diagnosed type 2 diabetes, 15 (36%) of 42 patients had hyperfiltration, compared with 8 (14%) of 57 patients and 10 (20%) of 50 patients whose duration of type 2 diabetes was between 1 and 5 years and from >5 to 10 years, respectively. With type 2 diabetes duration of >10 years, only 1 of 45 patients had hyperfiltration. Table 1 shows the baseline characteristics of the patients with (n = 34) and without hyperfiltration (n = 160) according to the duration of diagnosed type 2 diabetes. The duration of diagnosed type 2 diabetes had no effect on the degree of hyperfiltration as determined by GFR. RPF, and therefore filtration fraction, did not change. GFR and filtration fraction in the patients without hyperfiltration decreased when duration of type 2 diabetes was >10 years (P < 0.05 for all groups). RPF, however, did not change.

Patients with hyperfiltration were younger than their counterparts matched for duration of diagnosed type 2 diabetes <1 year (P = 0.025), 1–5 years (P = 0.014), and >5–10 years (P = 0.021). Glucose control of the hyperfiltration group as assessed by HbA_{1c} and fasting plasma glucose at the time of the study was no different from that of the nonhyperfiltration group except for patients whose duration of

Table 1—*Baseline characteristics of African-American subjects with type 2 diabetes grouped according to duration of diagnosed disease and the presence of hyperfiltration or normal or decreased filtration*

Duration of type 2 diabetes (years)	GFR (ml · min^{-1} · 1.73 m^{-2})	RPF (ml · min^{-1} · 1.73 m^{-2})	Filtration fraction	HbA_{1c}	Age (years)	Normotension/ hypertension
<1						
Hyperfiltration	157.2 ± 5.1	571.6 ± 32.4	0.283 ± 0.012	1.26 ± 0.09	42.7* ± 2.6	13/2
Nonhyperfiltration	114.3 ± 3.6	383.6 ± 14.5	0.304 ± 0.011	1.19 ± 0.06	50.2* ± 1.8	14/13
1–5						
Hyperfiltration	154.0 ± 10.7	519.7 ± 74.8	0.313 ± 0.019	1.48 ± 0.09	37.5* ± 3.5	5/3
Nonhyperfiltration	109.5 ± 2.6	382.0 ± 11.4	0.292 ± 0.008	1.22 ± 0.07	48.6* ± 1.5	33/16
>5–10						
Hyperfiltration	151.0 ± 3.7	499.2 ± 26.5	0.308 ± 0.014	1.21 ± 0.14	46.5* ± 3.1	7/3
Nonhyperfiltration	107.9 ± 3.0	367.2 ± 13.8	0.302 ± 0.008	1.30 ± 0.07	55.3* ± 1.2	11/29
>10						
Hyperfiltration	142.4	481.5	0.296	1.31	59.0	0/1
Nonhyperfiltration	95.4 ± 4.7	362.5 ± 18.6	0.265 ± 0.006	1.35 ± 0.05	57.5 ± 1.1	12/32

Data are means ± SEM or proportions. *Within subgroups based on duration of type 2 diabetes, hyperfiltration patients are younger than nonhyperfiltration patients (P < 0.05).

Table 2—*Classification of urinary AERs of African-American subjects with type 2 diabetes grouped according to presence of hyperfiltration or normal or decreased filtration and of normotension or hypertension*

	Normoalbuminuria (AER <30 mg/24 h)	Microalbuminuria (AER 30–300 mg/24 h)	Proteinuria (AER >300 mg/24 h)
Hyperfiltration			
Normotension	15	1	0
Hypertension	5	2	0
Normal or decreased filtration			
Normotension	21	4	0
Hypertension	37	18	14

Data are *n*. AER was increased in only 3 of 23 hyperfiltration subjects versus 36 of 94 nonhyperfiltration subjects ($P = 0.02$).

type 2 diabetes was 1–5 years. In this group, the patients with hyperfiltration had a higher HbA_{1c} ($P = 0.045$) and fasting plasma glucose ($P = 0.0014$) than the nonhyperfiltration patients.

Neither systolic nor diastolic blood pressure differed between the hyperfiltration and nonhyperfiltration patients according to the duration of diagnosed type 2 diabetes. However, as duration of type 2 diabetes increased, the number of patients with hypertension and the level of blood pressure increased.

Albumin excretion rates (AERs) were obtained from 117 patients (Table 2). Patients with hyperfiltration were more likely to have normal AERs and be normotensive. Microalbuminuria was present in three patients with hyperfiltration, two of whom were hypertensive. None of the patients had clinical proteinuria. In patients without hyperfiltration, hypertensive patients were also likely to have microalbuminuria. All patients with proteinuria had coexisting hypertension.

Longitudinal data

Serial GFR and RPF studies and/or creatinine clearance measurements during a follow-up period of 1–18 years were performed in 13 of the hyperfiltration patients, and serum creatinine and urinary albumin measurements were available in 2 additional hyperfiltration patients. Table 3 shows the baseline and follow-up data for the 15 of the 34 patients whose initial study showed hyperfiltration. Figure 2 shows the longitudinal GFR and creatinine clearance measurements for 13 hyperfiltration patients. Among patients whose duration of type 2 diabetes was >10 years, only one had a creatinine clearance value that indicated impaired renal function. This person had a corresponding serum creatinine value of 2.3 mg/dl (203 μmol/l). The remainder of these patients, whose duration of diagnosed type 2 diabetes was up to 17 years, although they no longer had hyperfiltration, maintained their creatinine clearance within the normal range and had normal serum creatinine levels.

Table 4 shows the characteristics of 15 hyperfiltration patients at their last follow-up. Of the four patients whose duration of type 2 diabetes was 4–7 years, one developed hypertension and microalbuminuria, one developed hypertension, and one developed microalbuminuria. Of the 11 patients whose duration of type 2 diabetes was 10–18 years, one developed an elevated serum creatinine level and clinical proteinuria. Three patients had hypertension at the initial study, and four other patients developed hypertension dur-

Table 3—*Follow-up data from 15 of 34 subjects whose initial study showed hyperfiltration*

	Initial study			Follow-up GFR			Last follow-up				
Subject no.	Duration (years)	GFR	BP	Duration (years)	GFR	BP	Duration (years)	Serum creatinine	AER	BP	Creatinine clearance
1	<1	155.3	−	7	101.7	−	11	1.0 (88)	N	−	120.1
2	<1	194.4	+	4	179.0	+	10	0.9 (80)	M	+	162.4
3	<1	146.3	−	NA	NA	NA	7	1.0 (88)	M	−	NA
4	<1	148.6	−	3	146.0	−	5	1.0 (88)	N	−	130.7
5	<1	198.3	−	NA	NA	NA	5	0.7 (62)	M	+	157.2
6	<1	149.5	−	NA	NA	NA	7	0.7 (62)	N	+	146.8
7	2	144.0	−	9.5	157.3	−	13.0	0.8 (71)	N	−	123.9
8	2.5	141.9	+	8.0	145.6	+	15.0	0.7 (62)	P	+	NA
9	5	147.0	−	9.0	144.5	−	10.0	0.5 (44)	N	−	NA
10	6	155.8	−	9.0	182.9	−	13.0	1.0 (88)	N	−	NA
11	6	142.2	−	16.0	117.5	+	17.0	0.8 (71)	N	+	98.1
12	6	162.8	+	10.3	261.3	+	18.0	2.3 (203)	P	+	40.8
13	7	140.0	−	NA	NA	NA	14.0	0.9 (80)	*	−	NA
14	7	153.9	−	8.00	109.7	+	13.0	0.9 (80)	N	+	115.9
15	9	140.0	−	11.0	120.0	−	14.0	1.0 (88)	M	−	100.3

GFR and creatinine clearance are corrected for a surface area of 1.73 m^2. The duration of diagnosed type 2 diabetes at the tine of the study, the GFR or creatinine clearance (expressed in milliliters per minute per 1.73 square meters), the presence (BP +) or absence (BP −) of hypertension, serum creatinine (expressed in milligrams per deciliter, with micromoles per liter given in parentheses), and AER are presented. Some data were not available (NA). *Subject no. 13 has hematuria; thus, AER is not meaningful. N, normoalbuminuria (AER <30 mg/24 h); M, microalbuminuria (AER 30–300 mg/24 h); P, proteinuria (AER >300 mg/24 h).

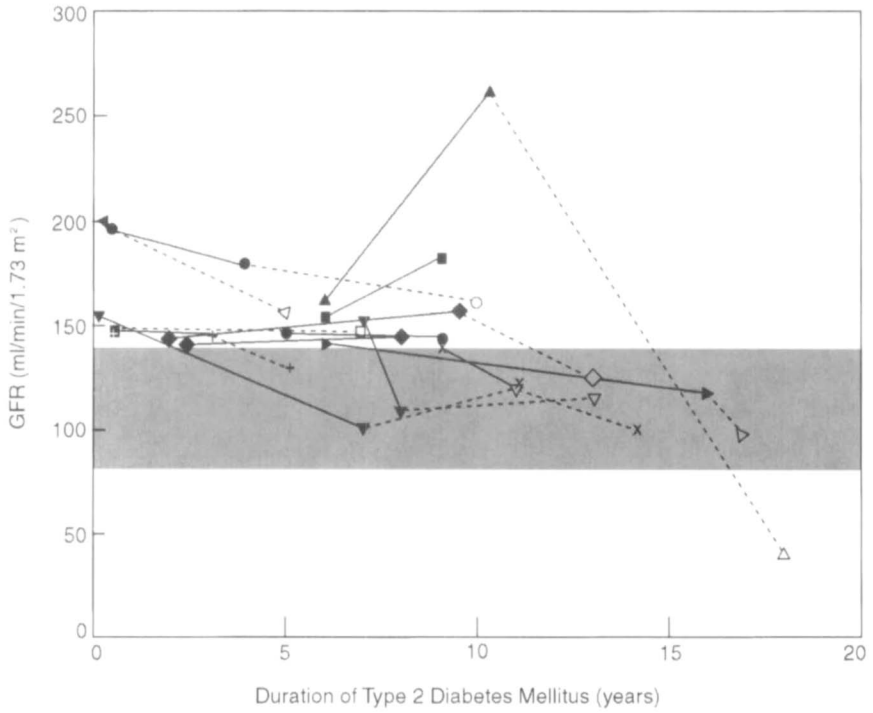

Figure 2—*The initial GFR (●, ▲, ■, ◆, —) and follow-up GFR (●, ▲, ■, ◆, —), and/or creatinine clearance (○, △, □, ◇, - - - -), are presented according to duration of diagnosed diabetes for each patient who initially showed hyperfiltration. Data are expressed in milliliters per minute per 1.73 square meters. Points above the shaded area are in the range of hyperfiltration (GFR or creatinine clearance ≥140 ml · min^{-1} · 1.73 m^{-2}) and points below the shaded area are in the range of impaired renal function (GFR or creatinine clearance <80 ml · min^{-1} · 1.73 m^{2}).*

ing the follow-up period. One of the previously hypertensive patients developed proteinuria. Of the three patients who developed microalbuminuria, one was previously hypertensive, one developed hypertension, and one remains normotensive.

CONCLUSIONS — In studies in type 1 diabetes, the role of hyperfiltration in microalbuminuria and the subsequent development of ESRD have been evaluated (1–6). We are studying renal function longitudinally in African-American patients with type 2 diabetes. This group has a 4.3-fold increase in ESRD compared with white subjects with type 2 diabetes.

Previously, we reported that in cross-sectional analyses of 194 African-American subjects with type 2 diabetes, the frequency of microalbuminuria increases with increasing duration of diagnosed diabetes (10,15). Proteinuria is present only in diabetic individuals with coexisting hypertension. Moreover, patients who have a long duration of diagnosed diabetes and have newly diagnosed hypertension are more likely to have impaired renal function as measured by elevated serum creatinine, clinical proteinuria, or GFR <80 ml · min^{-1} · 1.73 m^{-2}. These latter characteristics are similar to type 1 diabetic subjects who develop incipient nephropathy.

Our early preliminary study of renal function in type 2 diabetic African-Americans showed hyperfiltration in 25% of the 72 subjects (9,16). Because hyperfiltration has been identified as a very early marker of the risk for the development of diabetic nephropathy in type 1 diabetic subjects, we expanded our study population and assessed the impact of hyperfiltration on renal function. Our data show that in African-American patients with type 2 diabetes, *1*) hyperfiltration is present in 15 (36%) of 42 patients whose duration of diagnosed type 2 diabetes is <1 year, 2) hyperfiltration persists in 14–20% of patients who have a duration of diagnosed diabetes of up to 10 years, 3) at all durations of diagnosed diabetes, hyperfiltration occurs in younger patients, and 4) hyperfiltration does not appear to predict deterioration of renal function.

Studies in type 1 diabetic patients have shown conflicting results as to the link between early hyperfiltration and the subsequent development of nephropathy. In two of the early studies, Mogensen and Christensen (1,17) showed that hyperfiltration and early increases in AER could be predictive of further increases in AER. In a prospective study, Rudberg et al. (5) followed 64 type 1 diabetic patients for 8 years and reported that 17 of the 34 patients with hyperfiltration and normal AER developed incipient or overt nephropathy as measured by increased AER during the follow-up period. Hyperfiltration, however, was defined as a GFR of 125 ml · min^{-1} ·1.73 m^{-2}, which is lower than the GFR used to define hyperfiltration in this study as well as in other studies. Only 1 of the 19 patients with a GFR <125 ml · min^{-1} · 1.73 m^{-2} and a normal AER developed incipient nephropathy. In a prospective case-controlled study by Jones et al. (18), patients who initially had glomerular hyperfiltration (defined as GFR >135 ml · min^{-1} · 1.73 m^{-2}) were more likely to have a greater decrease in GFR

Table 4—*Characteristics at last follow-up of 15 African-American type 2 diabetic subjects with hyperfiltration at the initial study*

Duration of type 2 diabetes (years) at last follow-up	Patients	Elevated serum creatinine at last follow-up	Hypertension		AER at last follow-up		
			At initial study	At last follow-up	Normoalbuminuria	Microalbuminuria	Proteinuria
4–7	4	0	0	2	2	2	—
10–18	11	1	3	7	5	3	2

Data are *n*.

over a 5-year interval than were type 1 diabetic patients who had no hyperfiltration. However, hyperfiltration was not predictive of the development of incipient or overt nephropathy as indicated by an increase in AER or blood pressure. Lervang et al. (2) studied 29 type 1 diabetic patients who had studies of glomerular function 18 years earlier. At follow-up, the presence of increased urinary albumin excretion was associated with higher blood pressure and an increased frequency of proliferative retinopathy. Earlier glomerular hyperfiltration was not predictive of the development of increased urinary albumin excretion.

Hyperfiltration has also been identified in some type 2 diabetic populations. Silveiro et al. (19) showed that in a cross-sectional study, 15 (21%) of 71 type 2 diabetic patients attending an outpatient clinic of a university hospital in Brazil had an elevated GFR (>137.1 ml · min^{-1} · 1.73 m^{-2}) correlating with fasting plasma glucose and age. In a 5-year follow-up study of 32 normoalbuminuric type 2 diabetic patients with and without hyperfiltration, Silveiro et al. (20) showed that although patients with hyperfiltration had greater decreases in GFR than did patients with normal filtration, the development of increased AERs was associated with higher baseline AERs independent of the presence of hyperfiltration.

Schmitz (21), however, did not show hyperfiltration in type 2 diabetic patients from Denmark. Although patients with hyperglycemia had higher GFRs than did patients with better glycemic control, the GFRs were not in the hyperfiltration range. Moreover, the GFR in type 2 diabetic patients with albuminuria was not different from the GFR in normoalbuminuric type 2 diabetic patients. In a cross-sectional study of 197 type 2 diabetic patients followed at the Steno Diabetes Center in Denmark, Vedel et al. (22) reported that patients with microalbuminuria (n = 158) had a higher GFR (117 ± 24 ml · min^{-1} · 1.73 m^{-2}) compared with the normoalbuminuric group (n = 39) (99 ± 15 ml · min^{-1} · 1.73 m^{-2}) and nondiabetic control subjects (n = 20) (98 ± 21 ml · min^{-1} · 1.73 m^{-2}). Frank hyperfiltration, although present in 33% of the patients with microalbuminuria, was associated with younger age, shorter duration of diabetes, and higher HbA_{1c} in the group as a whole.

In the report of renal function of 163 type 2 diabetic patients from Italy, Gragnoli et al. (23) showed that hyperfiltration defined as GFR >139 ml · min^{-1} · 1.73 m^{-2} was present in 10 (6%) of the patients, all of whom were normotensive and 7 of whom were normoalbuminuric.

Pima Indians, who have a high rate of nephropathy associated with their high rate of diabetes, have not been shown to exhibit hyperfiltration when the GFR is corrected for surface area (24).

Lee et al. (25) reported on the renal function of 284 type 2 diabetic patients from Korea, 71 of whom had hyperfiltration (GFR >140 ml · min^{-1} · 1.73 m^{-2}). In this cross-sectional analysis, hyperfiltration correlated with shorter duration of diabetes and younger age and was not associated with glycemic control or microalbuminuria.

Thus, our data are similar to those of other studies of type 2 diabetic populations. If one uses the definition of hyperfiltration as GFR >139–140 ml · min^{-1} · 1.73 m^{-2}, hyperfiltration is more likely to be present in younger patients with shorter durations of diabetes. The data do not support the hypothesis that the presence of early hyperfiltration identifies the group of patients at greatest risk for the development of nephropathy. Microalbuminuria, however, remains a consistent predictor of the development of impaired renal function.

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