

DEVELOPMENT AND PROGRESSION OF RENAL DISEASE IN PIMA INDIANS WITH NON-INSULIN-DEPENDENT DIABETES MELLITUS

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ABSTRACT

Background Non-insulin-dependent diabetes mellitus (NIDDM) is a major cause of end-stage renal disease. However, the course and determinants of renal failure in this type of diabetes have not been clearly defined.

Methods We studied glomerular function at intervals of 6 to 12 months for 4 years in 194 Pima Indians selected to represent different stages in the development and progression of diabetic renal disease. Initially, 31 subjects had normal glucose tolerance, 29 had impaired glucose tolerance, 30 had newly diagnosed diabetes, and 104 had had diabetes for five years or more; of these 104, 20 had normal albumin excretion, 50 had microalbuminuria, and 34 had macroalbuminuria. The glomerular filtration rate, renal plasma flow, urinary albumin excretion, and blood pressure were measured at each examination.

Results Initially, the mean (\pm SE) glomerular filtration rate was 143 ± 7 ml per minute in subjects with newly diagnosed diabetes, 155 ± 7 ml per minute in those with microalbuminuria, and 124 ± 7 ml per minute in those with macroalbuminuria; these values were 16 percent, 26 percent, and 1 percent higher, respectively, than in the subjects with normal glucose tolerance (123 ± 4 ml per minute). During four years of follow-up, the glomerular filtration rate increased by 18 percent in the subjects who initially had newly diagnosed diabetes ($P=0.008$); the rate declined by 3 percent in those with microalbuminuria at base line ($P=0.29$) and by 35 percent in those with macroalbuminuria ($P<0.001$). Higher base-line blood pressure predicted increasing urinary albumin excretion ($P=0.006$), and higher base-line urinary albumin excretion predicted a decline in the glomerular filtration rate ($P<0.001$). The initial glomerular filtration rate did not predict worsening albuminuria.

Conclusions The glomerular filtration rate is elevated at the onset of NIDDM and remains so while normal albumin excretion or microalbuminuria persists. It declines progressively after the development of macroalbuminuria. (N Engl J Med 1996;335:1636-42.)

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IN the United States, one third of patients with end-stage renal disease who receive renal dialysis or transplantation have diabetes mellitus, and most of these have non-insulin-dependent diabetes mellitus (NIDDM).¹ The pathogenesis and progression of renal disease in patients with NIDDM have not been studied extensively, but such informa-

tion is crucial to determining the optimal approach to the treatment and prevention of the disease.

Pima Indians of the Gila River Indian Community in Arizona have the world's highest incidence of NIDDM,² and the incidence of end-stage renal disease in this group is more than 20 times that of the general U.S. population.³ As a result of a longitudinal epidemiologic study in this community, the onset of diabetes and its complications is recognized in many subjects. We studied six groups of Pima Indians who were selected to represent well-defined stages in the development of diabetes and renal disease. Base-line renal function was characterized in these subjects. Thus, when they were followed over a four-year period, the changes in glomerular function that occur during the development and progression of renal disease in patients with NIDDM could be determined.

METHODS

We recruited six groups of adult subjects with predefined characteristics: 31 who had had a normal oral glucose-tolerance test within three months of the base-line study and had no history of impaired glucose tolerance or diabetes; 29 with evidence of impaired glucose tolerance on a glucose-tolerance test within three months of the base-line study who had no history of diabetes; 30 who had newly diagnosed diabetes (the diagnosis was confirmed by a glucose-tolerance test) among subjects known to have had either normal or impaired glucose tolerance in the past three years; 20 who had had diabetes for at least five years who had normal urinary albumin excretion (ratio of urinary albumin [measured in milligrams per liter] to urinary creatinine [measured in grams per liter], <30); 50 who had had diabetes for at least five years and microalbuminuria (urinary albumin-to-creatinine ratio, 30 to 299); and 34 who had had diabetes for at least five years or more and macroalbuminuria (urinary albumin-to-creatinine ratio, ≥ 300). In each of these groups, participants were recruited in three age categories (18 to 30 years, 31 to 45 years, and 46 to 60 years) in order to minimize age differences between the groups. Subjects with elevated serum creatinine concentrations

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*The members of the Diabetic Renal Disease Study Group are listed in the Appendix.

(>1.3 mg per deciliter [115 μ mol per liter] for women and >1.5 mg per deciliter [133 μ mol per liter] for men) were ineligible, as were any potential subjects who were pregnant or had chronic debilitating conditions or any evidence of nondiabetic renal disease. Our goal was to recruit 30 subjects for each group except the group with microalbuminuria, for which 60 subjects were sought. The protocol was approved by the review boards of the National Institute of Diabetes and Digestive and Kidney Diseases, Stanford University, and the Cleveland Clinic Foundation and by the Tribal Council of the Gila River Indian Community. Each subject gave informed consent.

Diabetes and impaired glucose tolerance were defined on the basis of the results of an oral glucose-tolerance test with 75 g of glucose, according to criteria of the World Health Organization.⁴ Subjects who had had diabetes for five years or more were classified according to the geometric mean of four measurements of the ratio of urinary albumin to creatinine in four untimed urine samples collected at least a week apart. Those with a ratio below 30 were categorized as having normoalbuminuria; those with values of 30 to 299 as having microalbuminuria; and those with values at or above 300 as having macroalbuminuria.⁵

The subjects with diabetes of long duration and normoalbuminuria were followed for two years; all other subjects were followed for four years.⁶ The glomerular filtration rate and renal plasma flow were measured by the urinary clearance of iothalamate and aminohippurate, respectively, at base line and at four years in the subjects with normal glucose tolerance and at base line and two years in the group with diabetes of long duration and normoalbuminuria. These values were measured yearly in those with impaired glucose tolerance or newly diagnosed diabetes, and at intervals of six months in those with microalbuminuria or macroalbuminuria. At each follow-up examination, the urinary albumin-to-creatinine ratio was determined and blood pressure was measured while the subject was seated. Glycosylated hemoglobin was measured at the base-line examination.

Medical care was provided to the subjects, independently of the study protocol, by their usual Indian Health Service physicians. Diabetes was treated with dietary modification, oral hypoglycemic drugs, or insulin, as required to achieve glycemic control. The physicians were requested to avoid, if medically appropriate, drugs that might alter glomerular function, such as angiotensin-converting-enzyme inhibitors and nonsteroidal antiinflammatory drugs other than aspirin. The request that angiotensin-converting-enzyme inhibitors be avoided for subjects with macroalbuminuria was withdrawn as soon as their renoprotective effect in patients with insulin-dependent diabetes and advanced renal disease was demonstrated.⁷ At some time during the study, 31 subjects (18 percent of those who completed follow-up) received one or both of these classes of drugs. One patient with newly diagnosed diabetes, 1 with diabetes and normoalbuminuria, 3 with microalbuminuria, and 11 with macroalbuminuria received angiotensin-converting-enzyme inhibitors, and 3 with impaired glucose tolerance, 2 with newly diagnosed diabetes, 6 with microalbuminuria, and 2 with macroalbuminuria received nonsteroidal antiinflammatory drugs. Two patients with macroalbuminuria received both types of drugs.

Laboratory Methods

Albumin was measured in serum and urine by immunoprecipitation,⁸ or by enzyme-linked immunosorbent assay⁹ if the concentration was 0.2 mg per liter or lower. Creatinine concentrations in serum and urine were measured by a modification of the Jaffé reaction, glycosylated hemoglobin by agar gel electrophoresis,¹⁰ and plasma oncotic pressure by membrane osmometry. Iothalamate and aminohippurate were assayed with use of high-performance liquid chromatography.¹¹

Analysis of Glomerular Filtration

The ultrafiltration coefficient was calculated from a theoretical model that included the glomerular filtration rate, renal plasma

flow, and plasma oncotic pressure and an assumed value of 40 mm Hg for the glomerular transcapillary hydraulic-pressure difference, which cannot be measured directly in humans.¹¹⁻¹³ The ultrafiltration coefficient is defined as the product of effective hydraulic permeability and total glomerular capillary surface area of the kidneys.

Statistical Analysis

Clinical features of the subjects were compared among groups by analysis of covariance, with adjustment for age and sex. P values are reported either for overall comparisons among all groups or for pairwise comparisons, with the Bonferroni correction. Changes in group mean values for the glomerular filtration rate were assessed with a mixed-effects model.¹⁴ The relations between variables measured at base line and changes in the glomerular filtration rate or urinary albumin excretion were analyzed by linear regression, with adjustment for age and sex. Differences in the ultrafiltration coefficient between groups were analyzed with the Kruskal-Wallis test and those within groups over time were analyzed with the Wilcoxon signed-rank test.¹⁵

RESULTS

Base-Line Characteristics

The characteristics of the six groups (194 subjects; 81 men and 113 women) are shown in Table 1. The subjects with impaired glucose tolerance or newly diagnosed diabetes were heavier and had a greater body-mass index than those in the other groups ($P < 0.001$). The subjects with macroalbuminuria had a significantly higher mean arterial pressure than those in the other groups ($P = 0.002$); 21 percent of the subjects with macroalbuminuria were receiving treatment for hypertension, as compared with 10 percent or less of those in the other groups. The mean fasting serum glucose concentrations and glycosylated hemoglobin values differed significantly among the groups ($P < 0.001$); they were highest in the group with macroalbuminuria.

The mean glomerular filtration rate in the groups with newly diagnosed diabetes, normal albumin excretion, and microalbuminuria exceeded that in the group with normal glucose tolerance by 16 percent, 24 percent, and 26 percent, respectively ($P < 0.001$) (Table 1). The mean renal plasma flow was also higher in those groups, but it was significantly so only in those with microalbuminuria ($P = 0.002$). The glomerular filtration rate was proportionately more elevated than the renal plasma flow in the subjects with diabetes of long duration (≥ 5 years) and either normal albumin excretion or microalbuminuria. By contrast, the average glomerular filtration rate in the subjects with macroalbuminuria was lower than that in the other diabetic groups, and the renal plasma flow was somewhat lower. The plasma oncotic pressure, a force that opposes the rate of formation of glomerular filtrate, was lower in all groups with diabetes of long duration than in the other groups ($P < 0.001$).

Longitudinal Results

Follow-up was complete for 28 subjects with normal glucose tolerance (90 percent), 28 with impaired

TABLE 1. CHARACTERISTICS OF THE SUBJECTS AT BASE LINE, ACCORDING TO GROUP.*

CHARACTERISTIC	NORMAL GLUCOSE TOLERANCE (N = 31)	IMPAIRED GLUCOSE TOLERANCE (N = 29)	NON-INSULIN-DEPENDENT DIABETES MELLITUS			
			NEWLY DIAGNOSED DISEASE (N = 30)	NORMO- ALBUMINURIA (N = 20)	MICRO- ALBUMINURIA (N = 50)	MACRO- ALBUMINURIA (N = 34)
Sex (M/F)	12/19	11/18	13/17	8/12	19/31	18/16
Age (yr)	37±2	38±2	36±2	44±2	43±1	47±1
Weight (kg)	86±4	106±5	104±4	93±6	87±3	89±3
Body-mass index†	31.8±1.3	39.3±1.7	38.2±1.4	34.3±1.9	32.7±1.1	31.7±1.1
Duration of diabetes (yr)						
Mean	—	—	0.7	13.4	12.1	16.3
95% CI	—	—	0.005–3.1	8.3–23.8	6.3–23.8	8.0–24.9
Mean arterial pressure (mm Hg)	91±2	94±2	91±2	90±3	93±1	102±2
Antihypertensive-drug treatment (% of group)	0	0	7	5	10	21
Fasting serum glucose (mg/dl)‡	97±3	107±4	169±12	228±16	239±9	240±12
Glycosylated hemoglobin (%)§	5.9±0.1	6.3±0.1	8.5±0.4	11.4±0.6	11.9±0.3	12.2±0.3
Serum creatinine (mg/dl)¶	0.8±0.03	0.8±0.03	0.7±0.02	0.7±0.02	0.7±0.02	0.9±0.04
Urinary albumin-to-creatinine ratio						
Mean	8.0	12.4	13.2	10.9	87.7	1180
95% CI	5.1–12.6	8.7–17.5	9.2–19.0	8.8–13.5	72.8–106	844–1650
Glomerular filtration rate (ml/min)	123±4	135±7	143±7	152±9	155±7	124±7
Renal plasma flow (ml/min)	729±27	791±43	833±47	763±41	839±31	758±39
Filtration fraction	0.17±0.01	0.17±0.01	0.17±0.01	0.20±0.01	0.19±0.01	0.17±0.01
Plasma oncotic pressure (mm Hg)	24.0±0.3	24.0±0.4	23.6±0.4	21.6±0.5	22.7±0.3	21.0±0.4

*Plus-minus values are means ±SE. CI denotes confidence interval.

†The body-mass index was defined as the weight in kilograms divided by the square of the height in meters.

‡To convert values for glucose to millimoles per liter, multiply by 0.05551.

§Data were missing for one subject with impaired glucose tolerance, two with normoalbuminuria, and one with microalbuminuria.

¶To convert values for creatinine to micromoles per liter, multiply by 88.4.

||The filtration fraction was defined as the glomerular filtration rate divided by the renal plasma flow.

glucose tolerance (97 percent), and 24 with newly diagnosed diabetes (80 percent). During follow-up, impaired glucose tolerance developed in 7 subjects with normal glucose tolerance, and diabetes developed in 2; 12 of those with initially impaired glucose tolerance progressed to diabetes. Among the groups with diabetes of long duration, follow-up was complete in 16 subjects with normoalbuminuria (80 percent), 46 with microalbuminuria (92 percent), and 30 with macroalbuminuria (88 percent). Of the 22 subjects who did not complete the study, 5 died, congestive heart failure developed in 1 after a myocardial infarction, and 16 withdrew from the study.

During the four-year follow-up period, the glomerular filtration rate increased by 14 percent in the subjects with impaired glucose tolerance (P=0.008); the increase was 35 percent in the 12 subjects in this group in whom diabetes developed. It increased 18 percent in those with newly diagnosed diabetes (P=0.008) and did not change significantly in the subjects with diabetes of long dura-

tion and normal urinary albumin excretion (change, +2 percent) or in those with microalbuminuria (change, -3 percent) (Fig. 1 and 2). Glomerular filtration declined by 35 percent in subjects with macroalbuminuria (P<0.001); the average decline was 0.93 ml per minute per month; renal insufficiency developed in nine (30 percent) of these subjects (serum creatinine concentration, ≥2.0 mg per deciliter [177 μmol per liter]), and end-stage renal disease developed in one, who was treated with dialysis.

The geometric mean urinary albumin-to-creatinine ratio in the groups with impaired glucose tolerance and newly diagnosed diabetes remained in the normal range, changing less than 20 percent during the four years of follow-up. In the group with diabetes of long duration and normal urinary albumin excretion, the ratio increased by 75 percent (from 10.3 to 18.0) over a period of two years (P=0.08). During the four-year period, the ratio increased by 101 percent (from 84.9 to 170.9) in those with microalbuminuria (P=0.003) and by

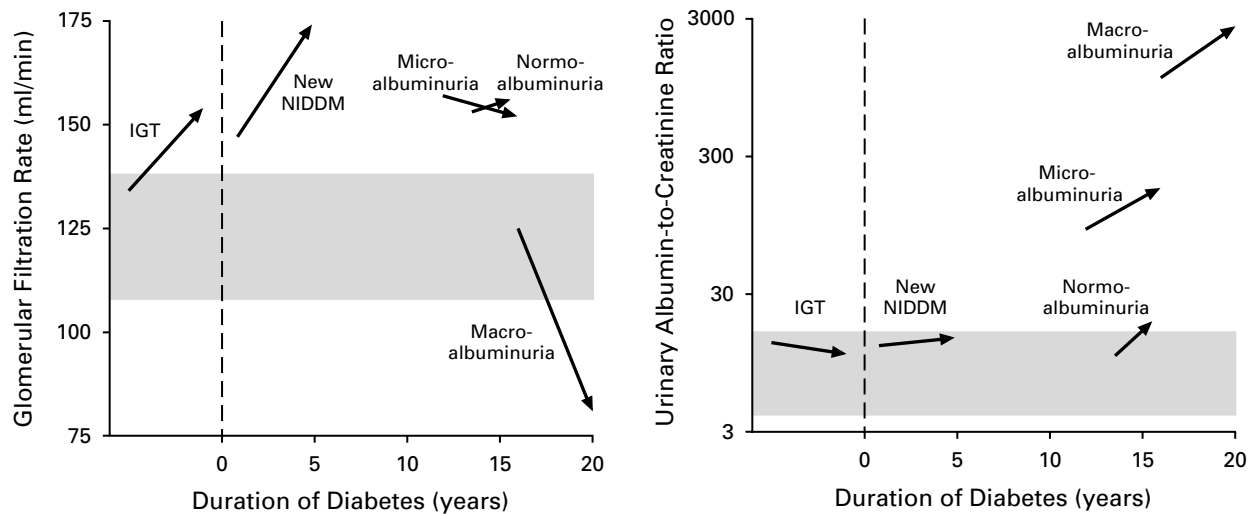


Figure 1. Changes in the Mean Glomerular Filtration Rate and Median Urinary Albumin-to-Creatinine Ratio from Base Line to the End of Follow-up in Subjects with Impaired Glucose Tolerance (IGT), Newly Diagnosed Non-Insulin-Dependent Diabetes Mellitus (New NIDDM), NIDDM and Normal Urinary Albumin Excretion (Normoalbuminuria), NIDDM and Microalbuminuria, and NIDDM and Macroalbuminuria.

Each arrow connects the value at the base-line examination and the value at the end of follow-up. The dashed line indicates the time of diagnosis, and the shaded area the 25th through 75th percentiles of values in subjects with normal glucose tolerance. Albumin was measured in milligrams per liter and creatinine in grams per liter.

133 percent (from 1123 to 2621) in those with macroalbuminuria ($P < 0.001$) (Fig. 1). Macroalbuminuria developed in 17 subjects with microalbuminuria (37 percent), as compared with 1 subject with newly diagnosed diabetes ($P = 0.003$).

In the diabetic subjects, the urinary albumin excretion at base line predicted the change in glomerular filtration ($r = -0.57$, $P < 0.001$) (Fig. 3). Among the 70 diabetic subjects who initially had normal albumin excretion or microalbuminuria, higher base-line blood pressure predicted increasing urinary albumin excretion ($r = 0.33$, $P = 0.006$), but neither the base-line serum glucose concentration ($P = 0.75$) nor the base-line glomerular filtration rate ($P = 0.21$) predicted such changes.

Factors related to worsening glomerular function were examined separately in the subjects with macroalbuminuria. Higher renal plasma flow, urinary albumin excretion, and body-mass index at base line each predicted a more rapid decline in the glomerular filtration rate, but the fasting serum glucose concentration, blood pressure, and glycosylated hemoglobin values did not. When these variables were examined together by multiple linear regression analysis, the significant predictors of declining glomerular filtration rate were higher urinary albumin excretion ($P = 0.01$) and higher renal plasma flow ($P = 0.01$). An additional 50 ml per minute in renal plasma flow was associated with an additional decline of 0.12 ml per minute per month (95 percent confidence interval, 0.03 to 0.21) in the glomerular filtration rate.

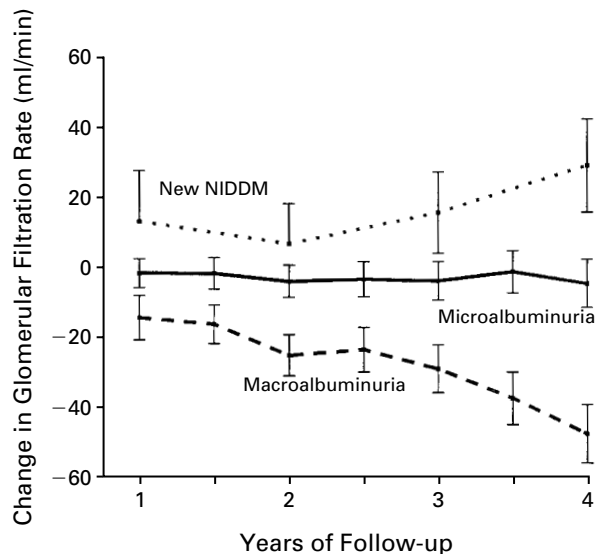


Figure 2. Mean (\pm SE) Change in the Glomerular Filtration Rate from Base Line during Four Years of Follow-up in Subjects with Newly Diagnosed NIDDM, NIDDM and Microalbuminuria, and NIDDM and Macroalbuminuria.

Lower error bars have been omitted where necessary to avoid overlap.

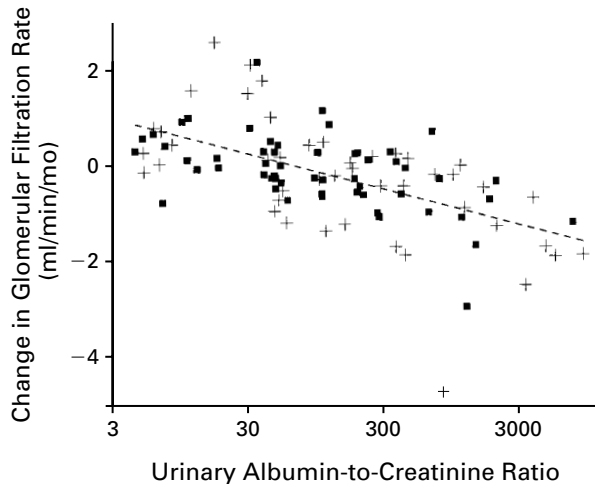


Figure 3. Changes in the Glomerular Filtration Rate in Individual Diabetic Subjects in Relation to Their Base-Line Urinary Albumin-to-Creatinine Ratio.

The scale for the ratio is logarithmic. Men are indicated by plus signs, and women by squares. The dashed line is the regression line for the relation between the slope of the glomerular filtration values and the albumin-to-creatinine ratios ($r = -0.57$, $P < 0.001$).

The glomerular ultrafiltration coefficient in the diabetic groups with normal albumin excretion and microalbuminuria was similar to that in subjects with normal glucose tolerance (11.8 ml per minute per millimeter of mercury) and did not change significantly during follow-up (Table 2). In the group with macroalbuminuria, the ultrafiltration coefficient was 40 percent lower than in the group with normal glucose tolerance at base line ($P < 0.001$), and it declined by a further 28 percent during the ensuing four years ($P = 0.002$).

DISCUSSION

Changes in glomerular function during the course of renal disease in subjects with NIDDM are difficult to evaluate because of uncertainties about the onset of diabetes and its protracted course and because of a high prevalence of nondiabetic renal disease in some populations.¹⁶ Among Pima Indians, details of the onset and duration of diabetes are known with greater certainty than is the case in other populations, and nearly all renal disease is attributable to diabetes.³ Previous studies of NIDDM in this population indicate that proteinuria and renal failure are common; that proteinuria develops more frequently in subjects with diabetes of long duration, hypertension, poor glycemic control, albuminuria, and hypercholesterolemia; and that microalbuminuria is a strong predictor of subsequent proteinuria.^{3,5,11,17,18}

The present study demonstrates that, in Pima Indians, NIDDM is characterized by glomerular hyperfiltration, both in those with newly diagnosed disease and in those with long-standing diabetes, except in the presence of macroalbuminuria; this pattern is consistent with the hypothesis that hyperfiltration causes progressive glomerular damage.^{19,20} However, the base-line glomerular filtration rate in the diabetic subjects predicted neither increasing urinary albumin excretion nor declining glomerular filtration during four years of follow-up, suggesting that hyperfiltration itself is not the principal factor in the development or progression of nephropathy. Higher urinary albumin excretion at base line, however, did predict increasing albuminuria and, in subjects with macroalbuminuria, declines in the glomerular filtration rate; these findings suggest that enhanced protein flux across the glomerular capillary wall contributes to progressive glomerular damage.²¹ Proteinuria also predicts the progression of renal disease in patients with nondiabetic renal disease.^{22,23}

Despite similar renal plasma flow and lower plasma oncotic pressure, the glomerular filtration rate was lower in the group with macroalbuminuria than in the other diabetic groups, indicating that either the transcapillary hydraulic-pressure difference or the ultrafiltration coefficient must be lower among subjects with macroalbuminuria. Because the mean arterial pressure and serum glucose concentration were higher in the group with macroalbuminuria, it is unlikely that the transcapillary hydraulic-pressure difference was lower. Even if we assume that the transcapillary hydraulic-pressure difference was the same, the computed ultrafiltration coefficient in the group with macroalbuminuria was 40 percent lower at base line than that in the group with normal glucose tolerance and declined by a further 28 percent over a period of four years. A preliminary analysis of glomerular structure in some of the subjects with macroalbuminuria revealed marked widening of the glomerular basement membrane and the epithelial foot processes,²⁴ features that are consistent with depressed permeability and a lower ultrafiltration coefficient.²⁵ Moreover, in subjects with macroalbuminuria a substantial fraction of glomeruli had global sclerosis, a characteristic not observed in the remaining diabetic groups²⁴ and one that would further reduce the glomerular ultrafiltration coefficient in the subjects with macroalbuminuria.

Although urinary albumin excretion increased and macroalbuminuria developed in 37 percent of the subjects with microalbuminuria, no significant changes in the glomerular filtration rate or the renal plasma flow were observed in this group. This lack of change presumably reflects the long time and the substantial changes in urinary albumin excretion that are required to reduce the ultrafiltration capacity of the glomeruli.

TABLE 2. GLOMERULAR FUNCTION AT BASE LINE AND AFTER FOUR YEARS IN SUBJECTS WHO HAD HAD DIABETES FOR AT LEAST FIVE YEARS AND MICROALBUMINURIA OR MACROALBUMINURIA.*

VARIABLE	MICROALBUMINURIA (N=46)		MACROALBUMINURIA (N=30)	
	AT BASE LINE	AT 4 YR	AT BASE LINE	AT 4 YR
Mean arterial pressure (mm Hg)	93±1	91±1	102±2	103±2
Serum creatinine (mg/dl)†	0.68±0.02	0.67±0.02	0.90±0.04	2.01±0.35‡
Urinary albumin-to-creatinine ratio				
Mean	84.9	171‡	1123	2621‡
95% CI	69.6–103	105–278	782–1613	1747–3931
Glomerular filtration rate (ml/min)	157±7	152±6	125±8	81±10‡
Renal plasma flow (ml/min)§	845±32	797±25	767±43	560±49‡
Ultrafiltration coefficient (ml/min/mm Hg)§				
Median	10.5	10.8	7.1	3.8
95% CI	9.6–11.8	10.0–12.9	6.0–8.9	2.3–6.7‡

*Plus-minus values are means ±SE. CI denotes confidence interval. One man with macroalbuminuria progressed to end-stage renal disease after three years. In this subject, a final study was performed after 32 months of follow-up, and for the longitudinal analyses he was considered to have completed follow-up.

†To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

‡P<0.05 for the comparison with the base-line value.

§Data on renal plasma flow and the ultrafiltration coefficient were missing for one subject with macroalbuminuria at the four-year examination.

In summary, glomerular hyperfiltration is present in patients with NIDDM from the onset of the disease until the time macroalbuminuria appears. After the development of macroalbuminuria, the glomerular filtration rate declines at least as rapidly as has been reported in subjects with insulin-dependent diabetes, despite adequate control of blood pressure. A progressive loss of intrinsic ultrafiltration capacity is the predominant cause of the declining glomerular filtration rate. The relation between the higher renal plasma flow at base line and more rapid decline in glomerular filtration in the subjects with macroalbuminuria suggests that the decline occurs because glomerular hyperperfusion no longer compensates for the reduced ultrafiltration capacity. Although the incidence of renal failure attributable to NIDDM is higher among the Pima Indians than in some other populations, the similar risk factors and outcome strongly suggest that the determinants and progression of renal disease in Pima Indians are similar to those in other groups of patients with NIDDM.

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APPENDIX

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