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Incidence of proteinuria in type 2 diabetes mellitus in the Pima Indians

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Incidence of proteinuria in type 2 diabetes mellitus in the Pima Indians. Little is known of the natural history of nephropathy in type 2 (non-insulin-dependent) diabetes, yet type 2 diabetes is a major cause of end-stage renal disease in the United States. The incidence rate of heavy proteinuria was determined in Pima Indians participating in a longitudinal population study of diabetes and its complications. Heavy proteinuria was defined by a urine protein (g/liter) to urine creatinine (g/liter) ratio ≥ 1.0 (≥ 113 mg protein/mmol creatinine), a level which corresponds to a urine protein excretion rate of about 1 g/day. The incidence rates of proteinuria in diabetic Pimas were 4, 12, 37, and 106 cases/1,000 person-years at risk in the periods 0 to 5, 5 to 10, 10 to 15, and 15 to 20 years after the diagnosis of diabetes. The cumulative incidence rates were 2%, 8%, 23%, and 50% at 5, 10, 15, and 20 years, respectively. The duration of diabetes, severity of diabetes as determined by the degree of hyperglycemia and type of treatment, and blood pressure were risk factors for proteinuria. The presence of heavy proteinuria was strongly associated with the development of renal insufficiency, defined by serum creatinine ≥ 2.0 mg/dl (≥ 177 μmol/liter). The incidence of proteinuria in type 2 diabetes in Pima Indians was as high as that reported in type 1 diabetes in other populations and represents a frequent, serious complication of the disease.

The belief that renal disease develops more frequently in type 1 (insulin-dependent) than in type 2 (non-insulin-dependent) diabetes [1–3] is based primarily on studies in Caucasian populations which show that 30 to 60% of deaths in type 1 diabetes are attributable to renal failure [4–6], yet fewer than 5% of deaths in type 2 diabetes are attributable to this cause [7, 8]. Extensive studies of the natural history of nephropathy in patients with type 1 diabetes have permitted characterization of a course progressing to end-stage renal disease [9, 10]. The natural history of nephropathy in subjects with type 2 diabetes, however, has not been well described even though 80 to 90% of the diabetic population in the United States has type 2 diabetes, as do at least 50% of the diabetic patients receiving treatment for end-stage renal disease [4]. Some reports of the course of diabetic nephropathy have included subjects with both type 1 and type 2 diabetes [11, 12], whereas others have been limited to those with type 1 diabetes [6, 13, 14].

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Since 1965, Pima Indians living in the Gila River Indian Community in southern Arizona, USA have participated in a longitudinal study of diabetes and its complications. This tribe has the world's highest reported prevalence of diabetes (50% at ≥ 35 years of age) [15]. Pima Indians have diabetes which is not associated with insulin dependency, ketoacidosis, or islet-cell antibodies, and is, therefore, type 2 diabetes [16], even when it occurs in the young [17]. Diabetic nephropathy is the predominant form of kidney disease in this population and is similar in its clinical characteristics and classical pathologic features to that described in other populations [18]. It frequently results in end-stage renal disease, which develops in nearly 15 per cent of diabetic Pima Indians by 20 years duration of diabetes [19].

The purposes of the present study were: (1) to investigate the incidence of nephropathy as reflected by the presence of heavy proteinuria in a population with a high prevalence and relatively early age of onset of type 2 diabetes; (2) to compare the incidence of proteinuria in type 2 diabetes with that reported in type 1 diabetes; and (3) to identify possible risk factors for the development of proteinuria in subjects with diabetes.

Methods

Since 1965, all Pima Indians at least five years of age living in a defined area of the Gila River Indian Community in Arizona have been asked to participate in systematic biennial research examinations. These examinations included a modified oral glucose tolerance test, measurements of height, weight, and blood pressure, and collection of urine. After voiding, the patients were given a 75 g oral carbohydrate load (Glucola, Ames Division of Miles Laboratory Inc., Elkhart, Indiana or Dexcola, Custom Laboratories Inc., Baltimore, Maryland, USA). Two hours later, venous blood was drawn for plasma glucose and serum creatinine determinations, and a urine specimen was collected and screened for protein with bromphenol strips (Labstix, Miles Laboratory Inc.). Protein concentration was determined by the Shevky-Stafford procedure [20] on all specimens showing a trace or more of protein; the concentration of creatinine in the same urine specimen was determined; and the protein (g/liter) to creatinine (g/liter) ratio was calculated. Heavy proteinuria was defined by a P/C ratio ≥ 1.0 (or 113 mg protein/mmol creatinine). This ratio is equivalent to a total protein excretion rate of about 1 g per day [21, 22]. No other means of quantifying proteinuria, such as by repeated

Table 1. Incidence[a] of heavy proteinuria (P/C ≥1.0)

Age years	Sex[b]	Nondiabetic			Diabetic		
		Person-years	Cases	Incidence	Person-years	Cases	Incidence
5–24	M	10678	7	0.7	108	1	9.3
	F	12594	17	1.4	264	1	3.8
25–44	M	2866	1	0.3	1208	17	14.1
	F	4942	15	3.0	1580	23	14.6
45–64	M	1292	0	0.0	1116	28	25.1
	F	1640	3	1.8	2421	70	28.9
≥65	M	678	3	4.4	472	10	21.2
	F	520	3	5.8	710	30	42.3
Total		35210	49		7878	180	
Age-sex adjusted incidence				1.7			16.5
95% confidence interval				(1.1–2.4)			(12.2–20.8)

[a] Cases/1000 person-years at risk
[b] M = male, F = female

measurements over several months or by 24-hour urine collections, was routinely available in this large population study.

Diabetes was diagnosed at the first biennial examination at which the two-hour post-load plasma glucose was ≥ 200 mg/dl (11.1 mmol/liter) [23], or when the Indian Health Service Hospital serving the community found a post-prandial or two-hour post-load glucose concentration of ≥ 200 mg/dl (11.1 mmol/liter) [15]. Renal insufficiency was defined by a serum creatinine concentration ≥ 2.0 mg/dl (177 μmol/liter). Blood pressure was measured with a mercury sphygmomanometer with the subject resting supine. Systolic and diastolic pressures were taken by auscultation of the brachial artery.

Incidence, the rate at which persons at risk develop proteinuria, was expressed as the number of new cases of proteinuria per 1000 person-years at risk. Cumulative incidence rates of proteinuria in diabetic Pimas and in subjects from two other longitudinal studies of diabetic nephropathy were compared [13, 14]. Cumulative incidence rates were presented in the studies or derived from incidence rates [24] stratified by duration of diabetes. The cumulative incidence estimates the probability that proteinuria will develop by a certain duration of diabetes conditional on survival to that point. Sex, obesity, two-hour plasma glucose concentration at diagnosis, blood pressure, type of treatment, cigarette smoking, and age at diagnosis of diabetes were examined as risk factors for proteinuria. The effects of variables which change over time, such as age, duration of diabetes, blood pressure, and type of treatment, were assessed by stratification of person-years at risk of proteinuria. Age was categorized and changed at each subject's 5th, 25th, 45th, or 65th birthday (that is, at 20 year intervals starting at age 5 years, the earliest possible entry in the study); five-year diabetes duration categories were used starting at the date of diagnosis and changing at the 5-, 10- and 15-year anniversaries of that date; and variables such as blood pressure or type of treatment for diabetes, that were assessed at biennial examinations, were changed at each subsequent examination. Blood pressure measurements were categorized according to the observed values whether or not antihypertensive drugs were taken. Subjects were also stratified by factors which did not change with time, such as sex and age and plasma glucose at the time of diagnosis.

The incidence of renal insufficiency was computed by similar methods. New cases of renal insufficiency were defined by the first occurrence of a serum creatinine concentration ≥ 2.0 mg/dl (177 μmol/liter) at a biennial examination among persons with at least one previous biennial examination at which the serum creatinine concentration was below this level. Person-years at risk were stratified by duration of diabetes as described above and by the presence of heavy proteinuria. Proteinuria was classified as absent or present at each biennial examination according to whether the P/C ratio was < 1.0 or ≥ 1.0, and the person-years at risk of renal failure were accumulated for that category until the next biennial examination.

Incidence rates were age-sex adjusted by the direct method using the 1980 U.S. census population as a standard, as previously described [15]. Age-sex adjusted rates were calculated in categories of duration of diabetes and had to be restricted to subjects ≥ 25 years of age as the longer duration categories were not represented among younger subjects. Incidence rate ratios, adjusted for age, sex, and duration of diabetes, were computed by the Mantel and Haenszel procedure [25]; tests of linear association were computed by the Mantel extension test [26]. These analyses were modified for person-time denominators as suggested by Rothman and Boice [27].

Results

Among the diabetic subjects, 180 of the 480 persons at risk developed heavy proteinuria during 7,878 person-years of follow-up, and among nondiabetic subjects, 49 of 4,171 developed heavy proteinuria during 35,210 person-years of follow-up (Table 1). The age-sex-adjusted incidence of heavy proteinuria was 9.7 times as high in diabetic as in nondiabetic subjects (95% confidence interval = 6.1 to 15.3). In diabetic subjects, the incidence of heavy proteinuria increased with increasing age until ages 45 to 64 years in males and ≥ 65 years in females. Among diabetic subjects, the incidence rate was similar in men and women after adjustment for age and duration of diabetes (incidence rate ratio, men compared with women, =1.0, 95% confidence interval = 0.7 to 1.4). Among subjects ≥ 25 years of age with diabetes, the age-sex adjusted incidence rate increased from 4 cases per 1,000 person-years in those with less than 5 years duration to 106 cases per 1,000 person-years in those with ≥ 15 years duration (Fig. 1). Among all diabetic subjects, the

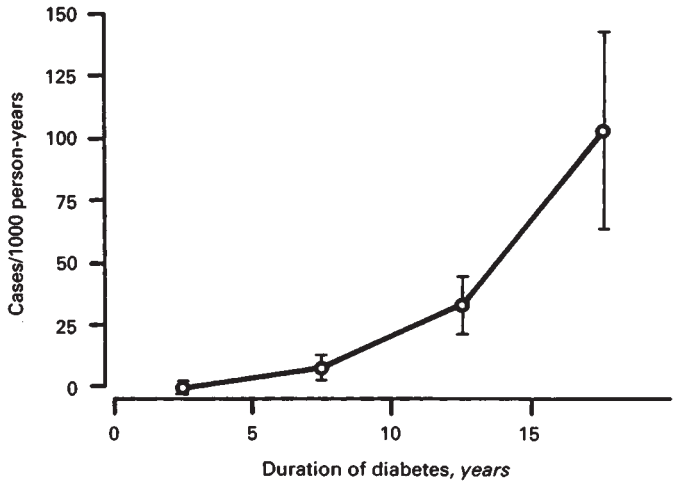

Fig. 1. *Incidence rates (and 95% confidence intervals) of heavy proteinuria by duration of diabetes.* Age-sex adjusted in subjects ≥ 25 years old.

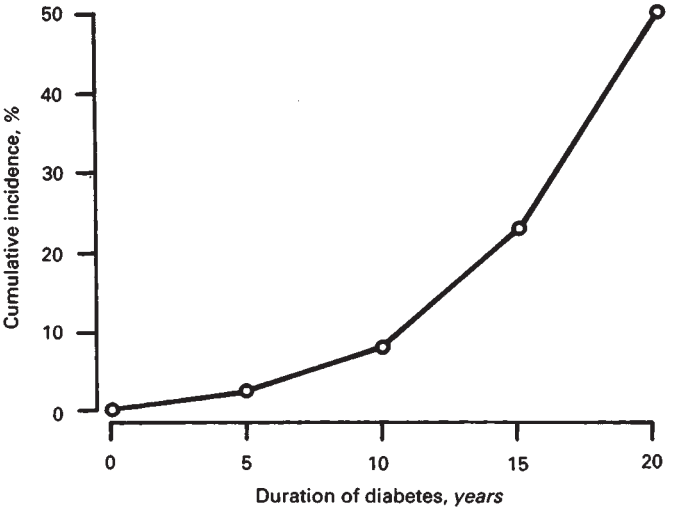

Fig. 2. *Cumulative incidence of heavy proteinuria in diabetic Pima Indians.*

cumulative incidence of heavy proteinuria as a function of duration of diabetes was 50% after 20 years (Fig. 2).

Table 2 shows the incidence rates of heavy proteinuria in diabetic subjects ≥ 25 years of age stratified by age and duration of diabetes. The incidence rates clearly increased with longer duration of diabetes in each age group, whereas within categories of duration of diabetes, the differences between age groups were small. After controlling for duration of diabetes there was no significant effect of age; whereas after controlling for age, the effect of duration was highly significant ($P < 0.001$).

Table 3 shows the incidence of renal insufficiency in diabetic subjects ≥ 25 years of age according to duration of diabetes and presence or absence of heavy proteinuria at the previous biennial examination. The age-sex-duration-adjusted incidence of renal insufficiency among diabetic subjects was 42 times as high in those with proteinuria as in those without (95% confidence interval = 24 to 75). Sex had no significant effect on the

Table 2. Incidence[a] of heavy proteinuria

Age *years*	Duration of diabetes *years*			
	0–5	5–10	10–15	>15
25–44	4.0	9.6	37.8	128.3
45–64	6.5	12.8	32.1	91.8
≥65	0.0	15.7	43.0	77.3

[a] Incidence in cases/1000 person-years, both sexes combined, in subjects ≥25 years old.

incidence of renal insufficiency after controlling for presence of proteinuria, age, and duration of diabetes (incidence rate ratio, men compared with women, =1.1, 95% confidence interval = 0.6 to 1.9).

Figure 3 shows the incidence of proteinuria according to the duration of diabetes in relation to several risk factors: a) age at diagnosis, b) two-hour post-load plasma glucose at diagnosis, c) type of treatment, and d) blood pressure. Subjects with a younger age at diagnosis of diabetes tended to have a higher incidence rate (Fig. 3A), but the differences among the groups shown were not statistically significant. There was a strong association between the severity of hyperglycemia at the time of diagnosis of diabetes and the incidence of proteinuria, ($P <$ 0.01, controlling for age, sex, and duration of diabetes, Fig. 3B). In each duration group, subjects with the highest two-hour post-load plasma glucose at diagnosis (≥ 450 mg/dl) had the highest incidence of proteinuria. Figure 3C shows the incidence of proteinuria according to the type of treatment: insulin, oral hypoglycemic agents, or no drug. The incidence rate was highest in subjects who were being treated with insulin, intermediate in those treated with oral agents, and lowest in those treated without drugs ($P < 0.001$, controlling for age, sex, and duration of diabetes). The incidence of proteinuria was significantly related to systolic blood pressure ($P < 0.001$, controlling for age, sex, and duration of diabetes, Fig. 3D) and to diastolic blood pressure (data not shown). The relationship with systolic blood pressure persisted after stratification by the simultaneous two-hour post-load plasma glucose concentration ($P < 0.001$, controlling for age, sex, duration of diabetes, and two-hour glucose). Neither obesity, as measured by body mass index, nor cigarette smoking was associated with an increased rate of proteinuria (not shown).

Discussion

Because of the high frequency and relatively early age of onset of type 2 diabetes in Pima Indians [15], it has been possible to examine the incidence of proteinuria with fewer problems than encountered in many studies of type 2 diabetes in older subjects. One of these problems is the high mortality from other causes that is encountered in many studies even at relatively short durations of diabetes. Because of the frequent onset of diabetes at an early age, many diabetic Pima Indians survive long enough after diagnosis to allow proteinuria to develop.

Among the Pimas, it has been possible to estimate the onset of diabetes with reasonable accuracy because glucose tolerance testing has been performed at approximately two-year intervals since 1965. Estimating disease onset in other populations is usually difficult in type 2 diabetes, as subjects may remain

Table 3. Incidence[a] of renal insufficiency (serum creatinine ≥2.0 mg/dl or ≥177 μmol/liter) by duration of diabetes and presence of heavy proteinuria at the previous biennial examination

Duration of diabetes *years*	Without proteinuria			With proteinuria		
	Person-yr	Cases	Incidence	Person-yr	Cases	Incidence
0–5	2811	0	0.0	124	1	12.7
5–10	2302	0	0.0	120	4	34.3
10–15	1490	1	0.3	182	11	57.9
15–20	716	3	2.1	174	15	56.0
≥20	246	1	5.1	128	14	101.4

[a] Age-sex adjusted cases/1000 person-years in subjects ≥25 years old.

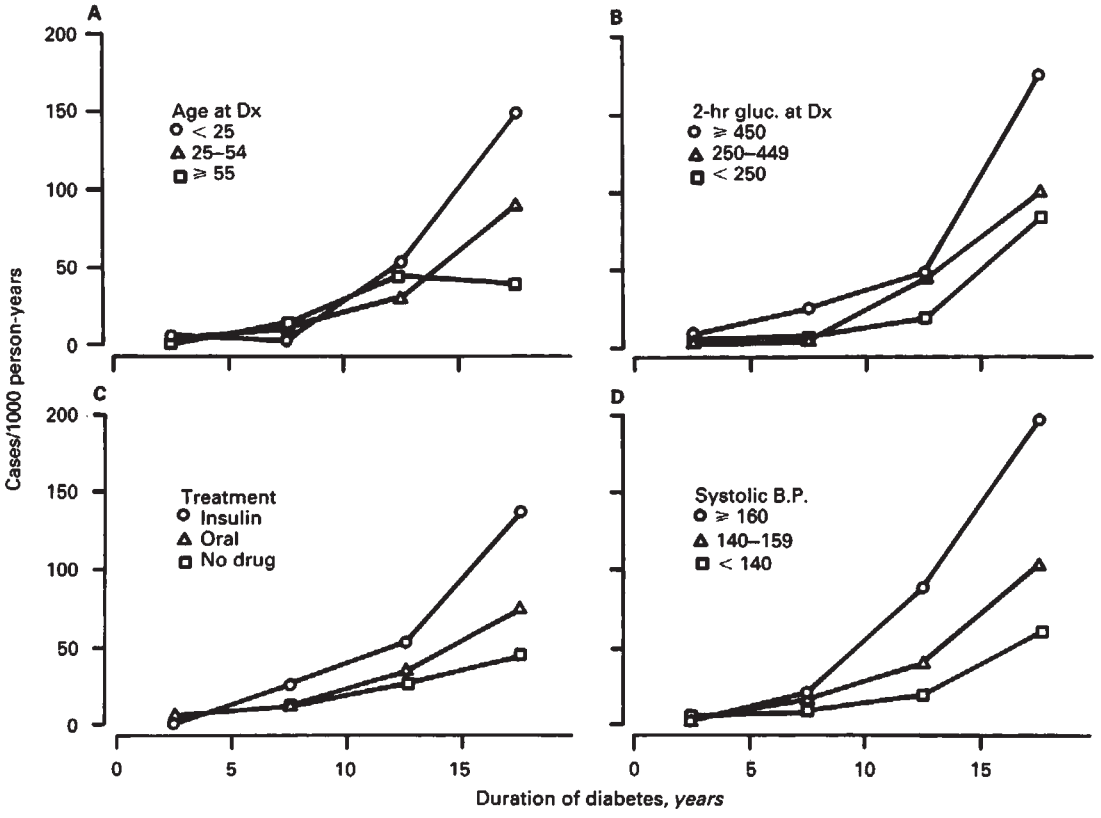

Fig. 3. *Incidence of heavy proteinuria in diabetic Pima Indians according to: (A) age at diagnosis (yrs.); (B) 2-hr post-load plasma glucose at diagnosis (mg/dl); (C) type of treatment for diabetes (insulin, oral hypoglycemic agent, or no hypoglycemic drugs); and (D) systolic blood pressure (mm Hg).*

asymptomatic for many years prior to recognition of their disease. Furthermore, as nearly all eligible Pimas have received systematic examinations [15], it has been possible to avoid the problems associated with the selective referral of patients with complications to centers specializing in diabetes care.

Heavy proteinuria in this study was defined by a urine protein (g/liter) to urine creatinine (g/liter) ratio of ≥ 1.0, which corresponds to a protein excretion rate of about 1 g/day [21, 22]. Persistent proteinuria, as detected by conventional clinical methods and used as an index of nephropathy in many studies of nephropathy in type 1 diabetes, is almost invariably present at this level. Moreover, the relative frequency of proteinuria as defined by a P/C ratio of ≥ 1.0 among diabetic compared with nondiabetic subjects indicates its specificity in diabetic subjects as an index of diabetes-related kidney disease.

The overall impact of renal disease associated with diabetes among the Pimas is considerable. Proteinuria predicts the development of renal insufficiency. Furthermore, end-stage renal disease, or death from renal disease, occurs 62 times as frequently among diabetic as among nondiabetic Pimas and occurs in nearly 15 per cent of Pimas after 20 years of diabetes [19]. Other causes of renal disease among diabetic subjects cannot be ruled out in all cases. However, given the present knowledge of the relative frequency of proteinuria, renal insufficiency, end-stage renal disease [19], and postmortem appearance of the kidneys in diabetic Pimas [18], it appears that proteinuria as defined in this study is, in most instances, attributable primarily to diabetic nephropathy.

In the present study the cumulative incidence of proteinuria in relation to duration of type 2 diabetes in Pima Indians was as

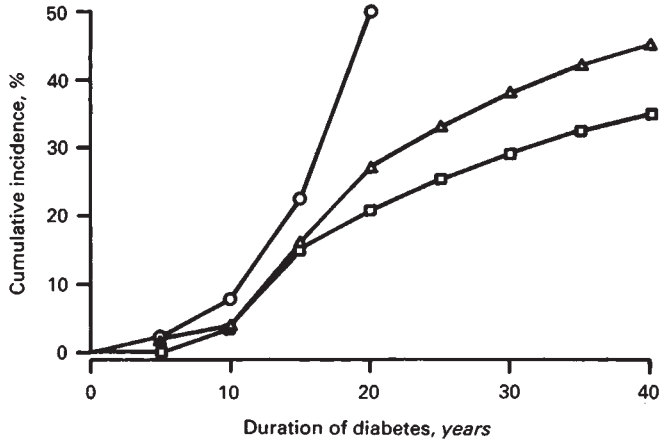

Fig. 4. Cumulative incidence of heavy proteinuria among diabetic subjects by duration of diabetes in three longitudinal studies: type 2 diabetic Pimas (○); type 1 diabetic subjects, Steno Memorial Hospital, Denmark (△); and type 1 diabetic subjects, Joslin Clinic, USA (□).

high as that reported in type 1 diabetes. The present findings were compared with results of two other studies (Fig. 4). In one of these, 907 type 1 diabetic patients diagnosed before the age of 31 years were followed for up to 40 years at the Steno Memorial Hospital in Denmark [13], and proteinuria was defined by protein excretion >500 mg/24 hr in at least four successive urine samples at least one month apart. In the other study, type 1 diabetic patients diagnosed before the age of 21 years were followed for up to 40 years at the Joslin Clinic in Boston, Massachusetts, USA [14], and proteinuria was defined by a urine protein concentration of ≥ 30 mg/dl in three or more successive urine collections or 1.0 g protein in a 24-hour urine collection. The cumulative incidence of nephropathy in type 1 diabetes in these studies was quite similar. In contrast, in the Pimas with type 2 diabetes, the cumulative incidence up to 20 years after the diagnosis of diabetes was even higher, reaching approximately 50% after 20 years.

These findings contrast with the common teaching that diabetic nephropathy is more common in type 1 than in type 2 diabetes [3, 4], a belief apparently derived from studies that show renal failure to be a more common cause of death in type 1 than in type 2 diabetes. For example, among all deaths of Joslin Clinic diabetic patients through 1968, the proportion ascribed to renal disease ranged from 46% in patients who had been diagnosed before 20 years of age (presumably with type 1 diabetes) to only 3% in those diagnosed at age 60 years or older (presumably with type 2 diabetes) [28]. As type 2 diabetes tends to occur at older ages, patients with type 2 diabetes are at higher risk of death from other causes and are, therefore, less likely to survive long enough to develop diabetic nephropathy and die as a result of it. While renal failure as a cause of death may be more frequent in type 1 than in type 2 diabetes, one cannot conclude that the risk of developing nephropathy in diabetes of a given duration is higher in type 1 diabetes. Indeed, the present data (Fig. 4) suggest that, as a function of the duration of diabetes, the incidence of nephropathy is at least as high in type 2 as in type 1 diabetes. Thus, the greater likelihood that death in subjects with type 1 diabetes will be attributed to renal disease appears to be due to their younger age, longer survival time, and lower risk of death from other causes rather than to the type of diabetes per se.

Whether the rate of proteinuria among Pima Indians is typical of that of patients of other ethnic origins with type 2 diabetes is unknown. Careful interpopulation studies of duration-specific incidence rates of diabetic nephropathy are necessary to resolve this question.

In contrast to results reported from Rochester, Minnesota [29], in this study an older age at diagnosis of diabetes was not associated with a higher duration-specific incidence of proteinuria. Several other risk factors did, however, predict the development of proteinuria among diabetic Pima Indians. A higher two-hour post-load plasma glucose at the time of the diagnosis of diabetes predicted a higher incidence of proteinuria, not only in the early years, but even after 15 to 20 years duration. These findings are in accord with other studies, both longitudinal and cross-sectional, which show an impressive relationship between nephropathy and the degree of hyperglycemia [30–32]. Whether the level of hyperglycemia per se is causally related to the development of nephropathy, or whether it is an indicator of the severity of a more basic metabolic defect related to diabetes, cannot be determined from the available data.

The severity of diabetes as judged by the type of treatment was also an important determinant of the risk of developing proteinuria in type 2 diabetes among the Pimas, similar to the previously reported association with the development of retinopathy [33]. Such an association might arise because patients with more severe hyperglycemia or with other complications might be more likely to receive insulin treatment. It seems unlikely that insulin is a causative factor for nephropathy, but, because treatment was not randomly assigned, the present data do not permit evaluation of this hypothesis.

Blood pressure was a risk factor for proteinuria in the present study and may be causally related to its development. Blood pressure was a risk factor for nephropathy in type 1 diabetes [34], and treatment of hypertension reduced the rate of progression of nephropathy in type 1 diabetes [35] and decreased albumin excretion rates in a group of patients including both types of diabetes [36]. The present finding that blood pressure predicts the development of proteinuria has several possible interpretations. Blood pressure may have increased as a result of renal disease of lesser severity than detected by the present definition of proteinuria, and the apparent predictive value of blood pressure for the development of heavy proteinuria may simply reflect an effect of progression of such renal disease. Alternatively, elevated blood pressure may result in increased susceptibility of the kidney to diabetes-related damage. Proteinuria may be the result of the combined insult, and blood pressure, therefore, may be causally related to the development of heavy proteinuria. This concept is consistent with evidence in type 1 diabetes that parental blood pressure is predictive of proteinuria in the offspring [37, 38] and that proteinuria is related to increased lithium-sodium countertransport velocity in red cells, which is thought to be a marker for idiopathic hypertension [38, 39]. It is also consistent with the finding in the Pima Indians that blood pressure measured prior to the development of diabetes predicts abnormal albuminuria after the development of diabetes [40]. Such a relationship might also account for the familial aggregation of proteinuria and renal

insufficiency among diabetic Pimas [41]. Whether hypertension is a consequence of early nephropathy, at a stage not detected in the present study, or whether it is a causative factor and present before any renal damage has occurred, remains to be determined. Nevertheless, the possibility that the treatment of hypertension may influence the risk and progression of nephropathy in type 2 diabetes, as it appears to do in type 1, clearly warrants investigation.

The incidence of proteinuria in type 2 diabetes among the Pima Indians is at least as high as that reported in type 1 diabetes. Furthermore, some of the risk factors for proteinuria identified in the present study, such as the duration of diabetes, the degree of hyperglycemia, and hypertension, appear to predict nephropathy in both types of diabetes. Whether the incidence of nephropathy in type 2 diabetes varies between populations is unknown, but as type 2 diabetes is by far the most common type of diabetes and is frequently the underlying cause of end-stage renal disease in the general population, the natural history and determinants of nephropathy in type 2 diabetes require further elucidation.

The finding that, as a function of the duration of diabetes, the incidence of proteinuria in type 2 diabetes is at least as high as in type 1 diabetes is ominous in view of the much greater frequency and apparently increasing incidence of type 2 diabetes worldwide. If, in the future, more persons develop type 2 diabetes at younger ages, and mortality rates from other causes such as ischemic heart disease decline, the burden of diabetes-related renal disease may increase dramatically. However, interventions, such as reduction of blood pressure, hyperglycemia, or perhaps, protein intake, which may be effective in ameliorating the course of renal disease in type 1 diabetes [42], may also affect the course of nephropathy of type 2 diabetes.

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