Diabetic Kidney Disease in Pima Indians

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OBJECTIVE— To describe the natural history of kidney disease in Pima Indians with NIDDM.

RESEARCH DESIGN AND METHODS— Review of previous studies describing diabetic kidney disease in this Native-American population and in other populations.

RESULTS— NIDDM is the leading cause of renal failure in Pima Indians, among whom the incidence of ESRD is 23 times that of the general U.S. population. The high incidence of NIDDM and its early onset in the Pima undoubtedly contribute to this difference. The incidence of overt nephropathy and ESRD, as a function of diabetes duration, is at least as high in Pima Indians with NIDDM as that reported in other populations with IDDM. Furthermore, nearly all of the excess mortality associated with NIDDM is found in individuals with overt nephropathy. Mild elevations of UAE, which may be present even shortly after the onset of diabetes, predict the development of overt nephropathy in diabetic Pimas. Additional predictors include high blood pressure, level of glycemia, duration of diabetes, family history of diabetic nephropathy, and type of diabetes treatment.

CONCLUSIONS— Diabetic kidney disease is a major cause of morbidity and mortality in Pima Indians. The natural history of diabetic kidney disease in this population is similar, in many ways, to the natural history described in individuals with IDDM.

NIDDM, a common chronic disease among Native Americans, is associated with a number of major complications. Notable among these, in terms of its impact on morbidity and mortality, is kidney disease. The incidence (rate of development of new cases) of ESRD in Native Americans is 2.8 times that of the general U.S. population, and 56% is related to diabetes (1). Differences in the incidence and age at onset of diabetes are primarily responsible for different rates of ESRD according to tribal group (Table 1). Navajo Indians have 4 times the incidence of treated ESRD as caucasians in the U.S., and 50% of the new cases are attributable to diabetes (2); Zuni Indians have 14 times the rate, and 33% is attributable to diabetes (3); and Pima Indians have 23 times the rate, and 93% is attributable to diabetes (4). Furthermore, among the Tohono O'odham (Papago) and Ute Indians, >70% of ESRD is found in diabetic individuals (5). The lower proportion of diabetic renal disease among the Zuni may be attributable to a competing type of renal disease that has not, as yet, been well characterized (3,6).

Pima Indians of the Gila River Indian Community in Arizona have one of the world's highest reported incidence rates of NIDDM (7), and the incidence of ESRD in this population is 23 times that in the U.S. (4). For the past 25 yr, the Pima Indians have participated in an epidemiological study of diabetes and its complications (8) that has provided much information on kidney disease associated with NIDDM.

This report reviews the natural history of the kidney disease of NIDDM, based on data from epidemiological studies of the Pima Indians. The development of renal disease is classified according to Mogensen et al.'s stages (9) for IDDM. The first stage of this classification, occurring with the onset of IDDM, is characterized by hyperfunction and renal hypertrophy. Stage 2 is manifested by morphological changes in the kidney without signs of clinical disease. Further progression of renal disease (stage 3, incipient diabetic nephropathy) is characterized by mildly elevated UAE not detectable by the usual dipstick tests which, in most cases, leads to persistent clinically detectable proteinuria (stage 4, overt diabetic nephropathy). Stage 5 is

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; ESRD, END-STAGE RENAL DISEASE; UAE, URINE ALBUMIN EXCRETION; OGTT, ORAL GLUCOSE TOLERANCE TEST; IGT, IMPAIRED GLUCOSE TOLERANCE; NGT, NORMAL GLUCOSE TOLERANCE; CI, CONFIDENCE INTERVAL.

Table 1—*Incidence of ESRD compared with the general U.S. population in several Native-American tribes*

Tribe	Incidence rate ratio (tribe/U.S.)	ESRD related to diabetes (%)
Navajo (2)	4	50
Zuni (3)	14	36
Tohono O'odham (5)	9	72
Ute (5)	22	78
Pima (4)	23	93

Numbers in parentheses are references.

ESRD with uremia. The earlier renal functional and morphological changes associated with IDDM have not been well defined in NIDDM and are not addressed. This review, instead, focuses on incipient and overt diabetic nephropathy and ESRD.

PIMA STUDY METHODS— The Gila River Indian Community is inhabited primarily by Pima and the closely related Tohono-O'odham Indians. Approximately every 2 yr since 1965, each person ≥5 yr of age, regardless of health, is asked to participate in a standardized examination that includes a medical history, physical examination, and glucose tolerance test after an overnight fast.

For the OGTT, glucose concentration is determined in venous plasma drawn 2 h after the ingestion of a 75-g carbohydrate load (Glucola, Ames Co., Elkhart, IN; or Dexcola, Custom Laboratories, Baltimore, MD; or Koladex, Custom Laboratories, Baltimore, MD). According to World Health Organization criteria for epidemiological studies (10), diabetes is diagnosed when the 2-h postload plasma glucose concentration is ≥11.1 mM (200 mg/dl). The date of diagnosis is determined from biennial examinations and review of clinical records (7).

Subjects are asked to void at the beginning of the OGTT, and a urine specimen is collected 2 h later. These collections are made predominantly between 0800 and 1200. Specimens are frozen, stored at −20°C, and assayed within 30 days for albumin concentration, with a nephelometric immunoassay using a monospecific antiserum to human albumin (11) and for creatinine concentration using the Jaffe method (12) as modified by Chasson et al. (13). A urine albumin/urine creatinine ratio (mg albumin/g creatinine) is used as an estimate of UAE rate (14–17). UAE, which has been measured at each examination since 1 July 1982, is considered to be abnormal if the albumin/creatinine ratio is ≥30 mg/g (18). In addition, since the initiation of the epidemiological studies, the presence of protein in the 2-h urine has been determined by dipstick (Labstix, Ames). All urine specimens containing at least a trace of protein on dipstick also are tested quantitatively for protein by the Shevky–Stafford method (19), and the urine protein/urine creatinine ratio is used as an estimate of the 24-h protein excretion. Proteinuria, defined as a urine protein/urine creatinine ratio ≥1.0 g protein/g creatinine, is equivalent to a total protein excretion rate of ~1 g/day (15,16). ESRD is attributed to diabetes only if the diabetic subjects have chronic persistent proteinuria and no clinical evidence of other renal disease by review of the clinical records (4).

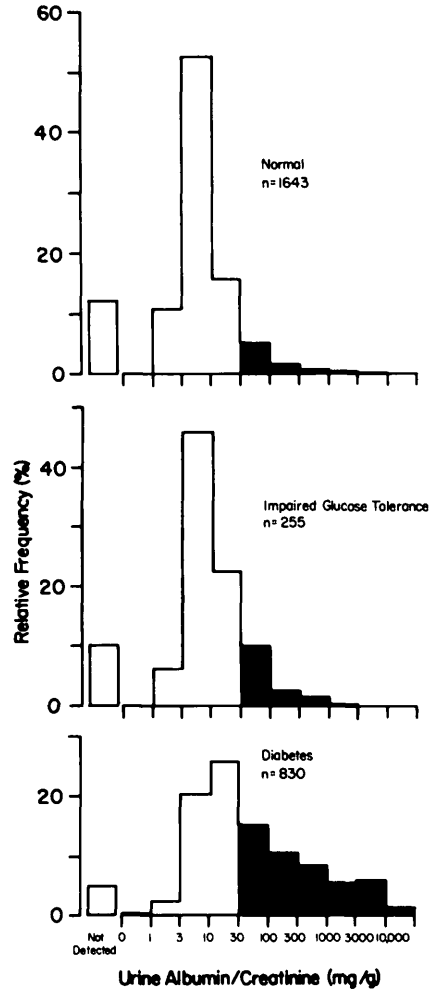

Figure 1—*Relative frequency (%) of urine albumin/creatinine ratios (on a log scale) in Pima Indians ≥15 yr of age, according to glucose tolerance. (■), Urine albumin/creatinine ratios considered to be abnormal.*

INCIPIENT DIABETIC NEPHROPATHY— UAE at concentrations in excess of normal, but undetectable by the usual clinical methods, generally is regarded as an early marker for renal disease and renal failure in IDDM (20–22) and clinical proteinuria in NIDDM (23–25). Diabetic Pima Indians, even those of recent onset, have higher UAE than nondiabetic Pimas (18). The distribution of UAE in diabetic Pima Indians, estimated from albumin/creatinine ratios, is shown in Fig. 1. In a cross-sectional study, 47% of the diabetic subjects had elevated UAE (≥30 mg/g), and 45% of these were below the levels reliably detectable by dipstick (albumin/creatinine ratio <300 mg/g). Moreover, among diabetic subjects, the prevalence increased with increasing duration of diabetes (Fig. 2), and elevated UAE was associated with age, level of glycemia, blood pressure, and treatment with insulin (18).

Besides being a common complication of NIDDM, elevated UAE is significantly more prevalent among Pima Indians with IGT than in those with NGT (Fig. 1). Keen et al. (26) first observed higher UAE rates in individuals who would now be considered to have IGT

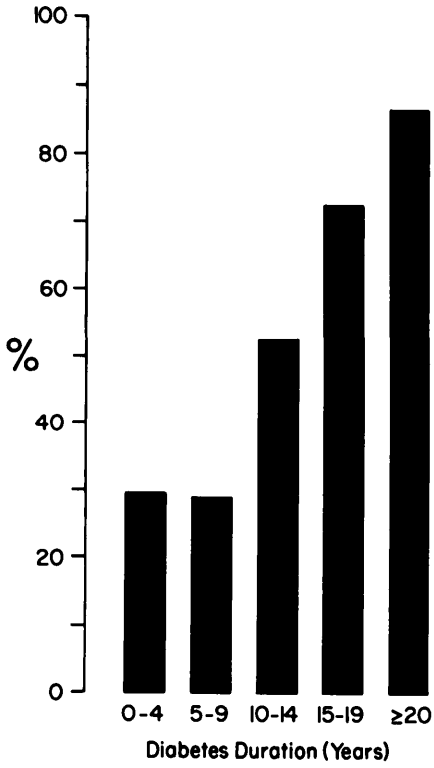

Figure 2—*Prevalence (%) of elevated UAE (urine albumin/creatinine ratio ≥30 mg/g) in diabetic Pima Indians ≥15 yr of age according to duration of diabetes. From Nelson et al. (18). © by Diabetologia.*

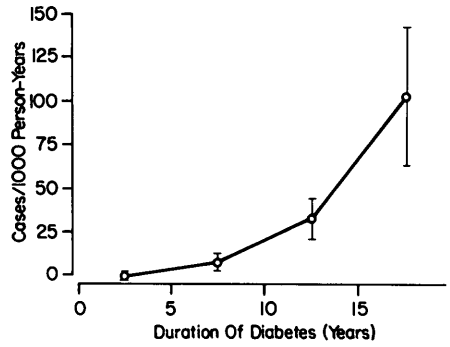

Figure 3—*Incidence rates (cases/1000 person-yr) and 95% CIs of overt nephropathy (urine protein/creatinine ratio ≥1.0 g/g) in diabetic Pima Indians ≥25 yr of age according to duration of diabetes. Rates were age and sex adjusted to the 1980 U.S. census population. From Kunzelman et al. (28). © by Kidney International.*

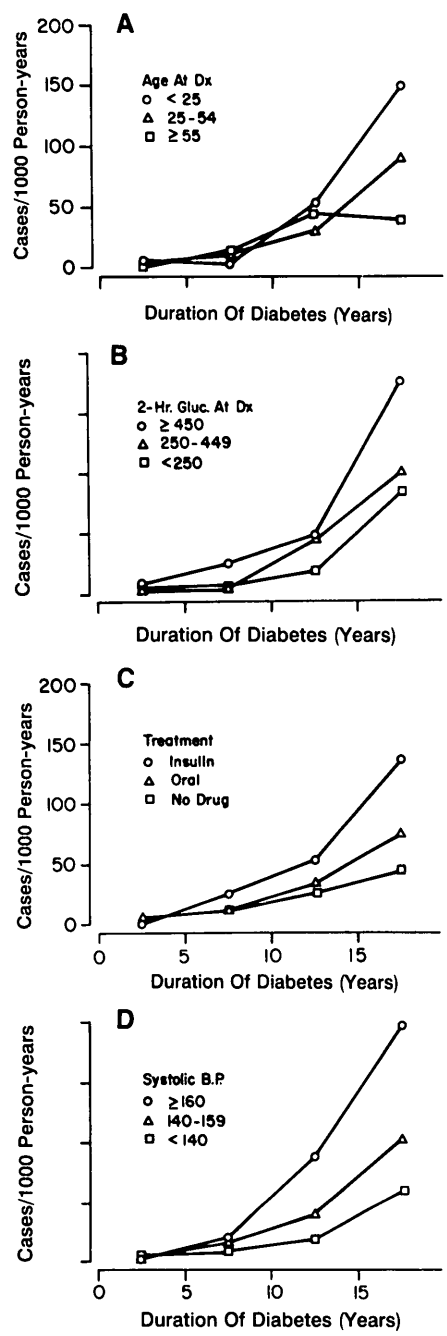

Figure 4—*Incidence (cases/1000 person-yr) of overt nephropathy (urine protein/creatinine ratio ≥1.0 g/g) in diabetic Pima Indians according to: (A) age (yr) at diagnosis of diabetes (Dx); (B) 2-h postload plasma glucose concentration (mg/dl) at diagnosis; (C) type of treatment for diabetes (insulin, oral hypoglycemic drug, or no hypoglycemic drugs); and (D) systolic blood pressure (mmHg). From Kunzelman et al. (28). © by Kidney International.*

than in those with NGT. In addition, Collins et al. (27) have reported higher prevalence of elevated UAE with IGT in Nauru. These findings indicate that in some individuals, hyperglycemia, even at levels below those diagnostic of diabetes, is associated with abnormalities of renal function and suggest that this abnormality might even precede the onset of diabetes (18). The prognostic significance of such abnormalities, however, is unknown.

Several factors associated with incipient diabetic nephropathy (18) predict the development of overt diabetic nephropathy and ESRD in Pima Indians with NIDDM (4,28). Two of these, high blood pressure and severity of hyperglycemia, are of great clinical interest because treatments for these conditions are available. Although not yet established, therapeutic intervention at this stage of disease might slow or even reverse the pathogenetic process responsible for the development of overt nephropathy and renal failure in diabetes (29–34). If so, identifying and treating such patients may have a major impact on the morbidity and mortality associated with diabetes.

OVERT DIABETIC NEPHROPATHY— The prevalence of overt nephropathy in the Pima Indians, defined by a urine protein/creatinine ratio ≥1.0 g/g, increased from 9% at the diagnosis of diabetes to 35% in subjects with ≥15 yr duration (28). The incidence also increased with increasing duration of diabetes (Fig. 3) (28). Similarly, the cumulative incidence of overt nephropathy in the primarily caucasian population of Rochester, MN, was 8% at the diagnosis of NIDDM and increased to 25% 20 yr after diagnosis (35). The relationship of several factors to the incidence of overt nephropathy in Pima Indians as a function of the duration of diabetes is shown in Fig. 4. Besides duration of diabetes, significant predictors of overt nephropathy in this population included 2-h postload glucose concentration at time of diagnosis of diabetes,

blood pressure, and type of diabetes treatment. In addition, subjects with an early age of onset tended to have a higher incidence than those developing diabetes at a later age. By contrast, in the Rochester, MN, population, older age at onset of diabetes and sex (being male), but not diabetes duration, were predictive of overt nephropathy (35). Nevertheless, the cumulative incidence of overt nephropathy in Pima Indians and in Rochester, MN, as a function of diabetes duration, was at least as high as reported in IDDM (28,35), and no decrease in the risk of overt nephropathy was seen in either population after 10–15 yr of diabetes as reported for IDDM (36,37). The frequency with which overt nephropathy leads to the development of renal failure in NIDDM, however, is not well documented in most populations.

An increase in blood pressure is observed with the development of diabetic nephropathy and usually is thought to be a consequence of the renal damage associated with diabetes. On the other hand, in Pima Indians, elevated blood pressure even before the onset of diabetes predicts elevated UAE after diabetes onset (38). Thus, the relationship between renal disease and blood pressure in diabetes is not entirely clear. Although higher blood pressure can be a consequence of diabetic renal damage, higher blood pressure also may contribute to its development.

Deterioration of renal function in overt diabetic nephropathy can be diminished by improving blood pressure control (39–43). Angiotensin-I-converting enzyme inhibitors have been advocated for use in hypertensive diabetic patients because of their effect on glomerular intracapillary hydrostatic pressure in experimental models (44,45). Studies that demonstrate long-term benefit from these agents, however, are not currently available. Moreover, beneficial effects in slowing the rate of deterioration of renal function in humans have been found with other classes of antihypertensive drugs (39–43). Thus, careful control of blood pressure appears to be beneficial in persons with diabetic renal disease, but the ideal choice of agents remains uncertain (46).

The severity of diabetes, as assessed in Pima Indians by the 2-h postload plasma glucose concentration at the time of diabetes diagnosis and by the type of diabetes treatment, predicts the development of overt nephropathy. The degree of metabolic control also correlates with the rate of deterioration of kidney function in subjects with diabetic nephropathy (47). Strict metabolic control, however, has not been shown to slow the rate of deterioration in persons with overt nephropathy (48–50), but intervention before the development of overt nephropathy may prove more effective.

Excessive protein intake is thought to cause renal vasodilation and glomerular hyperperfusion. The resulting increase in the glomerular transcapillary hydraulic pressure gradient is believed to cause proteinuria and glomerular damage in animals (51,52). Beneficial short-term effects on kidney function of protein-restricted diet have been reported (53–56), and in Pima Indians, the institution of a calorie-restricted diet has resulted in a reduction of proteinuria (11). Long-term studies are currently underway.

The presence of overt nephropathy in Pima Indians with NIDDM is a risk factor for renal insufficiency (28) and other diabetic complications, including lower-extremity amputations (57), background (58) and proliferative (59) diabetic retinopathy, overall mortality (60), and mortality from uremia, coronary heart disease, and other cardiovascular diseases (60,61). Indeed, nearly all of the excess mortality associated with diabetes in this population occurs in persons with clinically detectable proteinuria, and the age-sex–adjusted death rate in diabetic subjects without proteinuria is no greater than the rate in nondiabetic subjects (60). Thus, proteinuria is a marker not only for persons with diabetic renal disease, but identifies those with NIDDM at increased risk for a number of macro- and microvascular complications and for death. Similar findings have been observed in individuals with IDDM and suggest a common underlying cause for albuminuria and the other diabetic complications, both renal and extrarenal, associated with it (62).

Renal disease is familial in Pima Indians. Diabetic offspring who have at least one parent with diabetes and proteinuria are at substantially greater risk of having proteinuria than diabetic offspring whose diabetic parents do not have proteinuria (63). This susceptibility to renal disease may be inherited independently of NIDDM. The nature of this susceptibility, and the mechanism by which it enhances the likelihood of developing renal disease in persons with diabetes, however, is unknown. In IDDM, parental hypertension is associated with diabetic renal disease in the offspring (64,65), and increased sodium/lithium countertransport activity, a genetically determined marker for risk of hypertension, may be responsible for this relationship and may contribute to the development of diabetic nephropathy (65–67).

ESRD — Renal insufficiency (defined by serum creatinine concentration ≥177 μM [2.0 mg/dl]) develops at 42 times the rate in Pima Indians with proteinuria diagnosed at previous biennial examinations as in those without (28) and, with the development of renal insufficiency, many individuals experience a progressive decline in renal function ultimately leading to ESRD. The incidence of ESRD in Pima Indians is ~23 times that in the U.S. population (Table 1). About 95% of the ESRD in Pima Indians occurs in those with diabetes, and 97% of the ESRD among the diabetic subjects is attributable to diabetic nephropathy (4). Diagnosis of diabetic nephropathy is based on clinical rather than histological evidence; but, in a previous study, histological data were obtained by analysis of postmortem material from 105 Pima

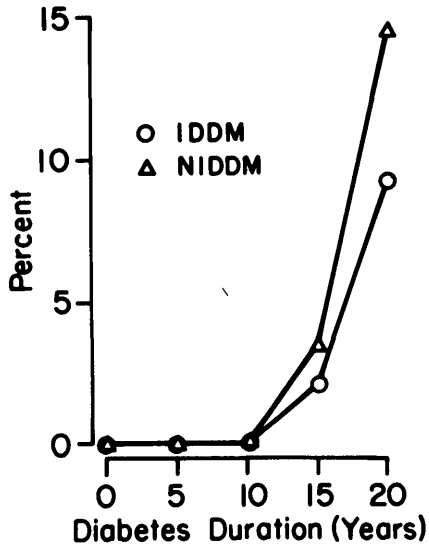

Figure 5—*Comparison of cumulative incidence (%) of ESRD attributed to diabetic nephropathy in Pima Indians with NIDDM and in subjects with IDDM followed at the Joslin Clinic, Boston, MA. From Nelson et al. (4). © by Diabetologia.*

Indians ≥15 yr of age, representing all Pimas in this age range that were autopsied between January 1961 and August 1971 on whom renal tissue and adequate clinical histories were available (68). Of the diabetic subjects, 65% had diffuse glomerulosclerosis and 56% had nodular glomerulosclerosis. The histological findings were indistinguishable from those described in other populations, and little other renal disease was noted among the diabetic subjects. Furthermore, nondiabetic Pima Indians had a low prevalence of renal disease. Thus, diabetic nephropathy was the predominant form of kidney disease in the Pima Indians.

The incidence of diabetic ESRD in Pima Indians is strongly related to blood pressure and the duration of diabetes, but not to age at onset of diabetes (4). Furthermore, the incidence of ESRD attributed to diabetic nephropathy in Pima Indians was at least as high as that reported in caucasian subjects with IDDM from the Joslin Clinic when duration of diabetes was taken into account (Fig. 5) (4). Such a comparison, however, is difficult to interpret because of age and racial differences between the two cohorts. In a study of Nebraska residents, Rettig and Teutsch (69) reported that the incidence of ESRD in IDDM was 16 times that in NIDDM. This has been taken to indicate that the incidence of ESRD is much lower in NIDDM than in IDDM, but incidence could not be analyzed as a function of duration. Hasslacher et al. (70) found the cumulative incidence of renal failure in a clinic-based population in Germany was similar for both types of diabetes when duration was considered. Similarly, the cumulative incidence of renal failure after 25 yr of diabetes for individuals in Rochester, MN, was 6.2% for those with NIDDM and 8% for those with IDDM (71).

CONCLUSIONS— Kidney disease is a frequent complication of NIDDM in Native Americans and is the major cause of ESRD. The rate of development of overt diabetic nephropathy and ESRD in Pima Indians is at least as high as reported in IDDM. Because the frequency of NIDDM in the Pimas and in many other Native-American tribes is extraordinarily high and is increasing, diabetic renal disease constitutes a major cause of morbidity and mortality, with serious consequences to health and longevity, and to health-care costs. Studies are currently being conducted in the Pima Indians to broaden our understanding of the pathophysiology of renal disease in NIDDM (72). These studies may unravel the mechanisms responsible for the development of diabetic nephropathy and point the way to better treatment. However, until major therapeutic advances are realized, aggressive antihypertensive therapy, in combination with improved metabolic control and, possibly, with dietary protein restriction, remain the treatments of choice. With no improvement in treatment, Native Americans will continue to experience a heavy burden of ESRD, and scarce resources will be depleted by the need to provide renal replacement therapy to an ever-increasing number of recipients.

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