Published in final edited form as:

Diabetes Res Clin Pract. 2008 November 13; 82(Suppl 1): S10–S14. doi:10.1016/j.diabres.2008.09.014.

Changing Course of Diabetic Nephropathy in the Pima Indians

Robert G. Nelson, MD, PhD, Meda E. Pavkov, MD, PhD, Robert L. Hanson, MD, MPH, and William C. Knowler, MD, DrPH

Diabetes Epidemiology and Clinical Research Section, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona.

Abstract

Pima Indians from the Gila River Indian Community in Arizona have a high incidence rate of type 2 diabetes, and kidney disease attributable to diabetes is a major cause of morbidity and mortality in this population. Since 1965, each member of the population at least 5 years of age is invited to participate in a research examination every other year. During the past 43 years, the overall incidence of diabetes in the Pima Indians has not changed, but the incidence of diabetes among those less than 15 years of age has increased nearly 6-fold, as an increasing prevalence and degree of obesity in the youth has shifted the onset of diabetes to younger ages. The rising frequency of diabetes in the youth has led, in turn, to the emergence in mid-life of the major complications of diabetes, including kidney disease. On the other hand, the introduction and widespread use of medicines to control blood pressure, reduce hyperglycemia, and block the renin-angiotensin system has led to improvements in the average blood pressure and glycosylated hemoglobin levels in the diabetic population. These countervailing forces have influenced the course of diabetic nephropathy in a generally favorable direction in the past few years, as evidenced by the decline in the overall incidence of end-stage kidney disease since 1990. A continued increase in the incidence of type 2 diabetes in youth, however, threatens to reverse this trend.

Keywords

Type 2 Diabetes; Diabetic Nephropathy; Epidemiology; Pima Indians; Secular Trends

Introduction

The Pima Indians who live in the Gila River Indian Community in Arizona have participated in a longitudinal study of diabetes and its complications since 1965. This study has shown that the prevalence of type 2 diabetes in this population is very high [1]. The low prevalence of diabetes even today among Pima Indians from Maycoba, Mexico [2,3], who share considerable genetic similarity with those in the U.S., supports the notion of an epidemic of diabetes in the Pima Indians from the Gila River Indian Community that coincides with increased contact with European-Americans and the ensuing change in lifestyle. Given the lack of systematic

Corresponding author: Dr. Robert G. Nelson, National Institutes of Health, 1550 East Indian School Road, Phoenix, AZ 85014-4972 USA. E-mail: rgnelson@mail.nih.gov Telephone: (602) 200-5205 Fax: (602) 200-5225.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest statement

None

screening for diabetes before 1965, an epidemic rise in the incidence of diabetes in the Pimas is difficult to confirm. Nonetheless, the available evidence suggests that an abrupt rise did occur between the 1930s and the beginning of screening [4,5], and this rise was followed by relatively stable incidence since that time, but with a shift to younger age at onset of diabetes as a consequence of increasing childhood obesity and increasing frequency of exposure to diabetes *in utero* [6–8]. This scenario, if true, may have profound implications on the course of diabetic kidney disease in this population and the relative importance of various risk factors for this complication of diabetes. The purpose of this review is to characterize the evolution of diabetic nephropathy in the Pima Indians and the role various factors may play in this evolution.

Research Design and Methods

In the longitudinal study, each member of the community who is ≥ 5 years old is invited to have a research examination approximately every 2 years, regardless of health. These biennial examinations include measurements of venous plasma glucose concentration, obtained 2 hours after a 75 g oral glucose load, and assessment for the complications of diabetes. Urinary albumin concentration is measured by nephelometric immunoassay [9] and urinary protein concentration by the Shevky-Stafford method [10]. Serum and urine creatinine concentrations are measured by a modification of the Jaffé reaction [11]. Proteinuria is defined by a protein-to-creatinine ratio ≥ 0.5 g protein/g creatinine, reflecting an estimated protein excretion rate of at least 0.5 g/day. Microalbuminuria is defined by an albumin-to-creatinine ratio of 30–299 mg albumin/g creatinine and macroalbuminuria by an albumin-to-creatinine ratio ≥ 300 mg/g. Diabetes was diagnosed by 1985 World Health Organization criteria [12]. Only the 2-hour post-load plasma glucose concentration (≥ 11.1 mmol/l) was used to diagnose diabetes at the research examinations, since this measurement was available throughout the longitudinal study period. The date of diagnosis is determined from these research examinations or from review of clinical records if diabetes is diagnosed in the course of routine medical care. Body mass index (BMI) is defined as weight divided by the square of height (kg/m^2). End-stage kidney disease is defined as initiation of chronic dialysis or death from diabetic nephropathy if dialysis is not available or refused and is ascertained independently of the research examinations. The cause of kidney failure in those receiving dialysis is determined by review of clinical records. The cause of death is determined by review of clinical records, autopsy reports and death certificates. Deaths are attributed to diabetic nephropathy if the ICD-9 code 250.4 is specified as the underlying or a contributing cause of death.

Changing Patterns of Type 2 Diabetes Incidence

Between 1965 and 2003, the average BMI in nondiabetic Pima Indians increased by 12 percent in the men and 19 percent in the women. An increase in obesity was found in all age groups, including children (Figure 1). Given the powerful effect of obesity on the development of type 2 diabetes [13], an increase in the incidence of diabetes might be expected as a consequence of the increasing obesity. Instead, the incidence rate of type 2 diabetes increased only among Pima Indians aged 5–14 years, decreased in those aged 25–34 years, and did not change significantly in other ages during the same period (Figure 2). These findings suggest that the vast majority of Pima Indians susceptible to diabetes were already developing the disease in the early years of the study, and the increasing obesity in youth combined with a nearly 4-fold increase in the frequency of exposure to diabetes *in utero* [7] simply shifted the onset of diabetes to younger ages in the most susceptible individuals [6]. The age-specific prevalence of diabetes increased over the same time in subjects < 25 years old, but did not show a similar trend in the older ages. Since mortality in young persons remained stable during this period, the increasing prevalence of diabetes in youth was believed to be largely attributable to the increasing incidence of diabetes in this age group [6].

If the incidence of diabetes did rise abruptly over a relatively short period prior to the onset of the longitudinal study, as we propose, the average duration of diabetes among community members would be shorter in the 1960s and 1970s than in the 1990s and beyond. In keeping with this hypothesis, the proportion of Pima Indians with diabetes of long duration has increased with time [14], and the increasing average duration of diabetes combined with a shift to younger age at onset could have important effects on the development of diabetic kidney disease.

Trends in Kidney Disease

The impact of the longer average duration of diabetes in recent years is illustrated by the rising incidence of proteinuria in diabetic Pima Indians [14]. The age-sex-adjusted incidence increased from 24.3 cases/1000 person-years in 1967–1978 to 38.9 cases/1000 person-years in 1991–2002. After adjustment for changes in the duration of diabetes, however, the incidence of proteinuria was stable, indicating that the incidence is rising in response to the increasing duration of diabetes [14]. Although the development of kidney disease has accelerated in the Pima Indians, its progression has slowed, with the incidence of end-stage kidney disease declining since 1990 (Figure 3). The slowing in the rate of progression of kidney disease may be due, at least in part, to improvements in the therapeutic management of diabetes and diabetic kidney disease.

Therapeutic Management

Clinical trials indicate that medicines that block the renin-angiotensin system (RAS) control hypertension, slow the progression from micro- to macroalbuminuria, increase the rate of regression from micro- to normoalbuminuria, and preserve the glomerular filtration rate in persons with diabetes [15–17]. Moreover, the effect is present regardless of the type of diabetes, stage of diabetic nephropathy, and duration of treatment [18]. In the Pima Indians, therapeutic interventions to block the RAS were introduced in November 1986, with only limited use until September 1989 [19]. Subsequently, their use increased gradually, as did the use of combination therapy for diabetes and blood pressure control [20]. Improved therapeutic management, involving increased use of RAS inhibitors as well as increased use of other blood pressure and hypoglycemic medicines are associated with significant improvements in average blood pressure and glycosylated hemoglobin levels in diabetic Pima Indians [20]. To what extent these enhancements in patient management have contributed to the decline in the incidence of end-stage kidney disease cannot be determined from an observational study, but most clinical trial data support a role for these agents in delaying the progression of kidney disease [15–18,21,22].

The decline in the incidence of kidney failure despite the increasing incidence of early kidney disease suggests that therapeutic advances, at least for the moment, are keeping pace with the changing pattern of diabetes in this population. The extent to which the increase in youth-onset diabetes affects the development of diabetic kidney disease, however, may negatively influence these relationships.

Effect of Youth-Onset Type 2 Diabetes

Diabetes in Pima Indian children and adolescents was first reported in the 1970s [23]. It is entirely type 2 and is characterized by the lack of insulin dependence [24], absent or low levels of islet cell and glutamic acid decarboxylase antibodies [25,26], and absence of strong linkage or association with maturity-onset diabetes of youth loci [27–29]. Of concern, the onset of diabetes in Pima Indians younger than 20 years of age is associated with a duration-specific incidence rate of proteinuria that is virtually identical to that in adult-onset type 2 diabetes, indicating that an equivalent duration of type 2 diabetes in a young person is as damaging to

the kidneys as it is in an older person [30]. Without a protective effect of youth, youth-onset diabetes is associated with a nearly 5-fold increase in the incidence of end-stage kidney disease between 25 and 54 years of age than in adult-onset disease (Figure 4) [31]. The more modest decline in the incidence of end-stage kidney disease in those below 45 years of age (Figure 3) may reflect less aggressive management of diabetic nephropathy in younger patients or lower death rates from competing causes of death, such as cardiovascular disease, or both.

Conclusions

Several factors influence the course of diabetic kidney disease in the Pima Indians. Among them is an increasing average duration of diabetes, which is responsible for a rise in the incidence of early kidney disease, and improvements in therapeutic management which are, for the moment, reducing the rate of progression and the overall incidence of kidney failure. A continued increase in the incidence of type 2 diabetes in youth combined with the impact of the increasing average duration of diabetes could ultimately reverse this trend as improvements in therapy are overshadowed by the greater number of patients developing kidney disease and the greater likelihood of surviving to kidney failure among those with an earlier onset of diabetes.

The prevalence of type 2 diabetes worldwide is expected to increase rapidly in the coming decades [32] and more populations are reporting the emergence of youth-onset type 2 diabetes in recent years [33]. If the experience in the Pima Indians is relevant to these populations, as we believe it is, substantially higher rates of kidney failure may occur in the coming years despite therapeutic advances.

References

1. Knowler WC, Bennett PH, Hamman RF, Miller M. Diabetes incidence and prevalence in Pima Indians: a 19-fold greater incidence than in Rochester, Minnesota. *Am J Epidemiol* 1978;108:497–505. [PubMed: 736028]
2. Ravussin E, Valencia ME, Esparza J, Bennett PH, Schulz LO. Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes Care* 1994;17:1067–1074. [PubMed: 7988310]
3. Schulz LO, Bennett PH, Ravussin E, Kidd JR, Kidd KK, Esparza J, Valencia ME. Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. *Diabetes Care* 2006;29:1866–1971. [PubMed: 16873794]
4. Joslin EP. The universality of diabetes. *JAMA* 1940;115:2033–2038.
5. Cohen BM. Diabetes mellitus among Indians of the American Southwest: its prevalence and clinical characteristics in a hospitalized population. *Ann Intern Med* 1954;40:588–599. [PubMed: 13139136]
6. Pavkov ME, Hanson RL, Knowler WC, Bennett PH, Krakoff J, Nelson RG. Changing patterns of type 2 diabetes incidence among Pima Indians. *Diabetes Care* 2007;30:1758–1763. [PubMed: 17468358]
7. Dabelea D, Hanson RL, Bennett PH, Roumain J, Knowler WC, Pettitt DJ. Increasing prevalence of type II diabetes in American Indian children. *Diabetologia* 1998;41:904–910. [PubMed: 9726592]
8. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* 1983;308:242–245. [PubMed: 6848933]
9. Vasquez B, Flock EV, Savage PJ, Nagulesparan M, Bennion LJ, Baird HR, Bennett PH. Sustained reduction of proteinuria in type 2 (non-insulin-dependent) diabetes following diet-induced reduction in hyperglycaemia. *Diabetologia* 1984;26:127–133. [PubMed: 6714534]
10. Shevky M, Stafford M. A clinical method for the estimation of protein in urine and other body fluids. *Archives of Intern Medicine* 1923;32:222–225.
11. Chasson AL, Grady HJ, Stanley MA. Determination of creatinine by means of automatic chemical analysis. *Tech Bull Regist Med Technol* 1960;30:207–212. [PubMed: 13692569]
12. World Health Organization. Diabetes Mellitus. Geneva: World Health Org.; 1985. (Tech. Rep. Ser. no. 727)

13. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. *Am J Epidemiol* 1981;113:144–156. [PubMed: 7468572]
14. Pavkov ME, Knowler WC, Bennett PH, Looker HC, Krakoff J, Nelson RG. Increasing incidence of proteinuria and declining incidence of end-stage renal disease in diabetic Pima Indians. *Kidney Int* 2006;70:1840–1846. [PubMed: 17003816]
15. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851–860. [PubMed: 11565517]
16. Brenner BM, Cooper ME, deZeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–869. [PubMed: 11565518]
17. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Amer P. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–878. [PubMed: 11565519]
18. Strippoli GF, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004;329:828. [PubMed: 15459003]
19. Sievers ML, Nelson RG, Bennett PH. Decrease in mortality from diabetic nephropathy in Pima Indians (letter). *Diabetes Care* 1996;19:777. [PubMed: 8799640]
20. Looker HC, Krakoff J, Nelson RG, Knowler WC, Hanson RL. Trends in treatment for diabetes and blood pressure: 1989–2003. *Diabetes* 2005;54:A611.
21. Fioretto P, Bruseghin M, Berto I, Gallina P, Manzato E, Mussap M. Renal protection in diabetes: Role of glycemic control. *J Am Soc Nephrol* 2006;17:S86–S89. [PubMed: 16565255]
22. Gaede P, Tarnow L, Vedel P, Parving HH, Pedersen O. Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria. *Nephrol Dial Transplant* 2004;19:2784–2788. [PubMed: 15328385]
23. Savage PJ, Bennett PH, Senter RG, Miller M. High prevalence of diabetes in young Pima Indians: evidence of phenotypic variation in a genetically isolated population. *Diabetes* 1979;28:937–942. [PubMed: 478185]
24. Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetes mellitus in Pima Indians: incidence, risk factors and pathogenesis. *Diabetes Metab Rev* 1990;6:1–27. [PubMed: 2192853]
25. Knowler WC, Bennett PH, Bottazzo GF, Doniach D. Islet cell antibodies and diabetes mellitus in Pima Indians. *Diabetologia* 1979;17:161–164. [PubMed: 389722]
26. Dabelea D, Palmer JP, Bennett PH, Pettitt DJ, Knowler WC. Absence of glutamic acid decarboxylase antibodies in Pima Indian children with diabetes mellitus. *Diabetologia* 1999;42:1265–1266. [PubMed: 10525671]
27. Hanson RL. the Pima Diabetes Genes Group. Genomic scan for markers linked to type II diabetes in Pima Indians. *Diabetes* 1997;46:51. [PubMed: 8971081]
28. Janssen RC, Bogardus C, Takeda J, Knowler WC, Thompson DB. Linkage analysis of acute insulin secretion with GLUT2 and glucokinase in Pima Indians and the identification of a missense mutation in GLUT2. *Diabetes* 1994;43:558–563. [PubMed: 8138061]
29. Muller YL, Infante AM, Hanson RL, Love-Gregory L, Knowler W, Bogardus C, Baier LJ. Variants in hepatocyte nuclear factor 4alpha are modestly associated with type 2 diabetes in Pima Indians. *Diabetes* 2005;54:3035–3039. [PubMed: 16186411]
30. Krakoff J, Lindsay RS, Looker HC, Nelson RG, Hanson RL, Knowler WC. Incidence of retinopathy and nephropathy in youth-onset compared with adult-onset type 2 diabetes. *Diabetes Care* 2003;26:76–81. [PubMed: 12502661]
31. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA* 2006;296:421–426. [PubMed: 16868300]

32. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047–1053. [PubMed: 15111519]
33. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GL, Saaddine J, Gregg EW, Williamson DF, Narayan KM. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 2000;136:664–672. [PubMed: 10802501]

Figure 1.

Mean BMI in nondiabetic Pima Indians by age, sex, and time period. The numbers below each graph represent the percent increase in mean BMI between the first and the third time period according to age group. **Reprinted with permission** [6].

Figure 2.

(A) Age-specific, sex-adjusted incidence rates of type 2 diabetes in three time periods. In each period, sex-adjusted incidence rates increased up to 55–64 years and then declined. (B) Incidence rate ratios (IRR) relative to the first time period. IRR2=incidence rate ratios in the second relative to the first period, IRR3=incidence rate ratios in the third relative to the first period. * $p_{\text{trend}} < 0.05$. **Reprinted with permission** [6].

Figure 3.

(a) Age-sex-adjusted incidence rates of end-stage kidney disease, defined by deaths from diabetic nephropathy (DN) and renal replacement therapy (RRT), in type 2 diabetic Pima Indians ≥ 25 years old. Incidence rates are calculated for 4-year intervals between 1967 and 2002. The number on top of each bar represents new cases of end-stage kidney disease. The combined height of the two bars represents the total incidence of end-stage kidney disease. (b) Sex-adjusted incidence of diabetic end-stage kidney disease for 9 4-year intervals, by age group. **Reprinted with permission** [14].

Figure 4. Sex-adjusted incidence (95% CI) of diabetic end-stage kidney disease by onset of diabetes and age group. **Adapted with permission** [31].