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Changing course of diabetic nephropathy in the Pima Indians

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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 have 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 (RAS) have lead 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.

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1. 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 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.

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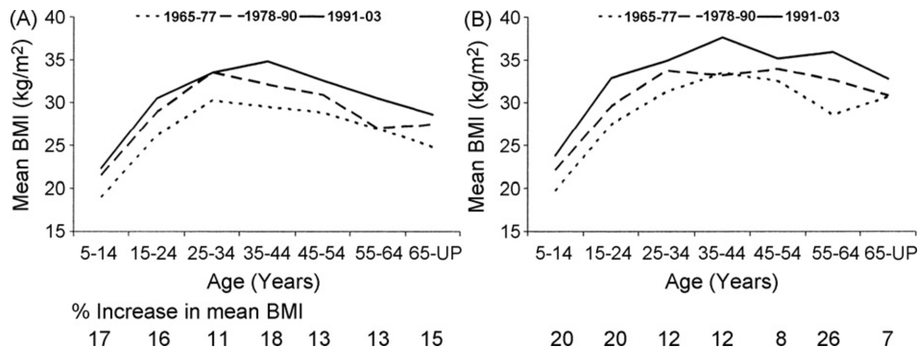

Fig. 1 – Mean BMI in nondiabetic Pima Indians by age, sex, and time period. The numbers below each graph represent the percent increase in mean BMI between the first and the third time period according to age group. Reprinted with permission [6].

2. 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 h 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-h 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.

3. Changing patterns of type 2 diabetes incidence

Between 1965 and 2003, the average BMI in nondiabetic Pima Indians increased by 12% in the men and 19% in the women. An increase in obesity was found in all age groups, including children (Fig. 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 (Fig. 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

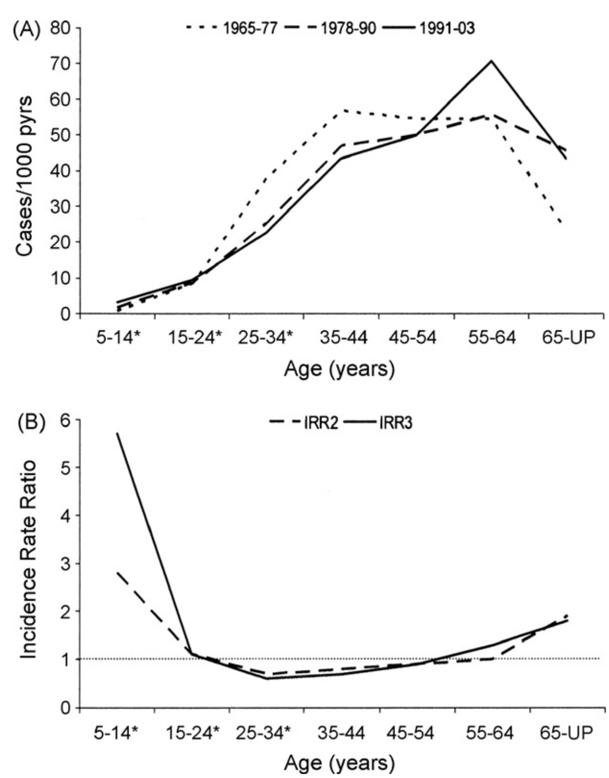

Fig. 2 – (A) Age-specific, sex-adjusted incidence rates of type 2 diabetes in three time periods. In each period, sex-adjusted incidence rates increased up to 55–64 years and then declined. (B) Incidence rate ratios (IRR) relative to the first time period. IRR2, incidence rate ratios in the second relative 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].