Comparison of the Effect of Plasma Glucose Concentrations on Microvascular Disease Between Pima Indian Youths and Adults

JONATHAN KRAKOFF, MD
ROBERT L. HANSON, MD, MPH
SAYUKO KOBES, BS
WILLIAM C. KNOWLER, MD, DRPH

OBJECTIVE — To examine whether the current adult guidelines for diagnosis of diabetes are applicable to youth (age <20 years).

RESEARCH DESIGN AND METHODS — We analyzed fasting plasma glucose (FPG) and 2-h plasma glucose (PG) in two groups of Pima Indians, youths aged 5–19 years and adults aged 20–34 years, in relation to the incidence of microvascular disease when subjects were reexamined at ages 25–39 (youths) and 40–54 (adults). Microvascular disease was defined as retinopathy or a urine protein-to-creatinine ratio ≥0.5 g.

RESULTS — An increase in the incidence of microvascular disease occurred at nearly the same level of glycemia in both groups. For youths, this increase occurred at FPG ~7.3 mmol/l and 2-h PG ~10.0 mmol/l; for adults, this increase occurred at FPG ~7.5 mmol/l and 2-h PG ~10.3 mmol/l. Sensitivity of the adult diagnostic guidelines of FPG ≥7.0 mmol/l and 2-h PG ≥11.1 mmol/l for the detection of microvascular disease was much lower (with higher specificity) in youths than in adults. Receiver operating characteristics (ROC) curve areas were lower for FPG and 2-h PG for youths, suggesting that microvascular disease was less strongly predicted by baseline glucose.

CONCLUSION — The current adult guidelines for diagnosis of diabetes are applicable to youth, as they identify a population at high risk of microvascular complications.

Diabetes Care 24:1023–1028, 2001

Since 1985, the World Health Organization (WHO) has defined diabetes as a fasting plasma glucose (FPG) of ≥7.8 mmol/l or a 2-h plasma glucose (PG) of ≥11.1 mmol/l. In 1997, the American Diabetes Association (ADA) recommended changing the diagnostic FPG to ≥7.0 mmol/l, keeping the 2-h PG value at ≥11.1 mmol/l (1). The WHO endorsed these recommendations in 1999 (2). The rationale for these diagnostic levels was based on separate population studies involving Pima Indians (aged ≥25 years) (3), National Health and Nutrition Examination Survey III participants (aged 40–74 years) (1), and Egyptians (aged >20 years) (4) evaluated for microvascular disease specific for diabetes. Recent data from the Pimas, which include subjects aged ≥15 years, confirmed those diagnostic levels for microvascular disease (5). However, there has been no evaluation of the specific applicability of those diagnostic levels to youth (age <20 years).

From the National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona.

Address correspondence and reprint requests to Jonathan Krakoff, Diabetes Arthritis and Epidemiology Section, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes, Digestive, and Kidney Disease, 1550 E. Indian School Rd., Phoenix, AZ 85014. E-mail: jkrakoff@mail.nih.gov.

Received for publication 10 October 2000 and accepted in revised form 5 March 2001.

Abbreviations: ADA, American Diabetes Association; FPG, fasting plasma glucose; MODY, maturity-onset diabetes of the young; ROC, receiver operating characteristics; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Examining the appropriateness of the current diagnostic guidelines for youth is important, as type 2 diabetes is clearly increasing in the pediatric population. Among Japanese school children, incidence of type 2 diabetes increased from 0.2 to 7.3 per 100,000 person-years from 1976–1995 (6). In Pima Indians, the age-specific prevalence of type 2 diabetes doubled in children aged 10–19 years from 1967–1976 and from 1987–1996 (7). In Northwest Ontario, age-adjusted prevalence for type 2 diabetes in children was 2.5 per 1,000 from 1978–1984 (8). Pediatric diabetes clinics in Cincinnati, OH, and Ventura, CA, found that type 2 diabetes accounted for 16–31% of all new cases of diabetes diagnosed under age 19 years (9,10). These data suggest that type 2 diabetes in children is an emerging epidemic (11).

Pima Indians have the highest recorded prevalence of diabetes in the world. Characterized by a strong genetic predisposition but without linkage or association to known maturity-onset diabetes of the young (MODY) loci, as well as lack of an insulin requirement for survival and absence of islet-cell antibodies, diabetes in the Pima Indian is entirely type 2 (12–16). In addition, GAD65Ab is not increased in Pima children diagnosed with diabetes (17).

Information on diagnostic glucose levels for youth is lacking. We examined the risk of microvascular disease in relation to fasting and 2-h glucose levels in a group of Pima children aged 5–19 years (youths) in comparison with a group of Pima young adults aged 20–34 years (adults).

RESEARCH DESIGN AND METHODS

— Members of the Gila River Indian Community have participated in a longitudinal study of diabetes and its complications since 1965. Every 2 years, residents of the community aged ≥5 years are asked to participate regard-

less of health status. Each participant undergoes a physical examination, which includes direct opthalmoscopy, a 75-g oral glucose tolerance test, and a spot urinalysis for assessment of creatinine and protein. The present analysis is restricted to subjects for whom both FPG and 2-h PG were measured. Because FPG was routinely collected beginning in 1975, the majority of exams included those from 1975 onward. The opthalmoscopy is performed without the examiner knowing the diabetes status of the participants. Pupils are dilated in participants aged ≥15 years. Retinopathy was defined as the presence of at least one microaneurysm, hemorrhage, or evidence of proliferative retinopathy. The technique and standards for diagnosing retinopathy have not changed over the period of the study. PG concentration was measured by the potassium ferricyanide method with an autoanalyzer or by the hexokinase method (in recent years). Subjects were asked to void at the beginning of the oral glucose tolerance test, and a urine specimen was collected 2 h later. Proteinuria was assessed using a dipstick test; throughout the study, all patients with levels of protein greater than or equal to trace on the urine dipstick had total urine protein measurement performed by the method of Shevky and Stafford (18). Urine creatinine was measured by the alkaline-picrate method. Nephropathy was defined by a protein-to-creatinine ratio ≥0.5 g.

Statistical analysis.

Our aim was to analyze the prognostic significance of hyperglycemia in youths. Therefore, we examined the relationship of glucose levels measured at age 5–19 years to the incidence of complications at age 25–39 years (youths). For comparison, we similarly examined the relationship of glucose in young adults aged 20–34 years to complications at age 40–54 years (adults). A baseline exam was defined for each group as the last exam within the initial age range, when FPG and 2-h PG were measured. A follow-up exam was defined as the last exam within the second age range, when an examination for retinopathy was performed and proteinuria was measured. Subjects with retinopathy or proteinuria at the baseline exam were excluded. Subjects were defined as having microvascular disease if they had retinopathy, nephropathy, or both at their last exam. Separate analyses for retinopathy and nephropathy were also performed. Analysis conducted with and without exclusion of subjects taking glucose-lowering medications revealed that excluded subjects came primarily from the extreme upper glucose categories in both groups, somewhat weakening the association between glucose and complications in both groups (data not shown). Because our goal was to examine the biological effect of glucose and because eliminating subjects on med-

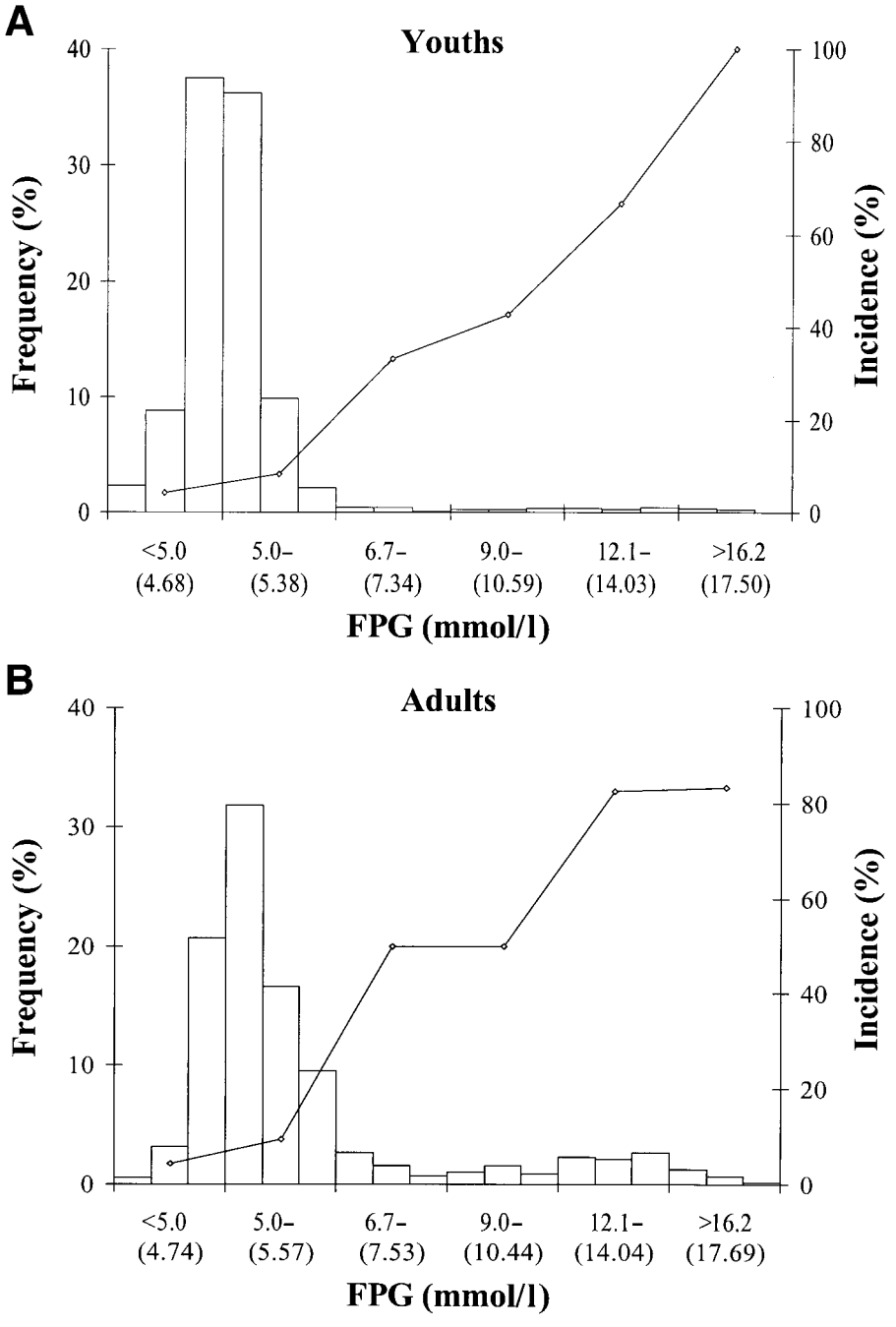

Figure 1—*Incidence of microvascular disease by FPG for youths* (A) *and adults* (B). *The x-axis represents FPG on a log scale. The top numbers represent the boundaries for the glucose categories. The numbers in parentheses represent the mean glucose for that category (e.g., for glucose category 5.0–6.6 mmol/l, mean = 5.38 mmol/l). The columns represent frequency distribution for FPG for all subjects (left y-axis). The line represents incidence of microvascular disease within each glucose category (right y-axis)*

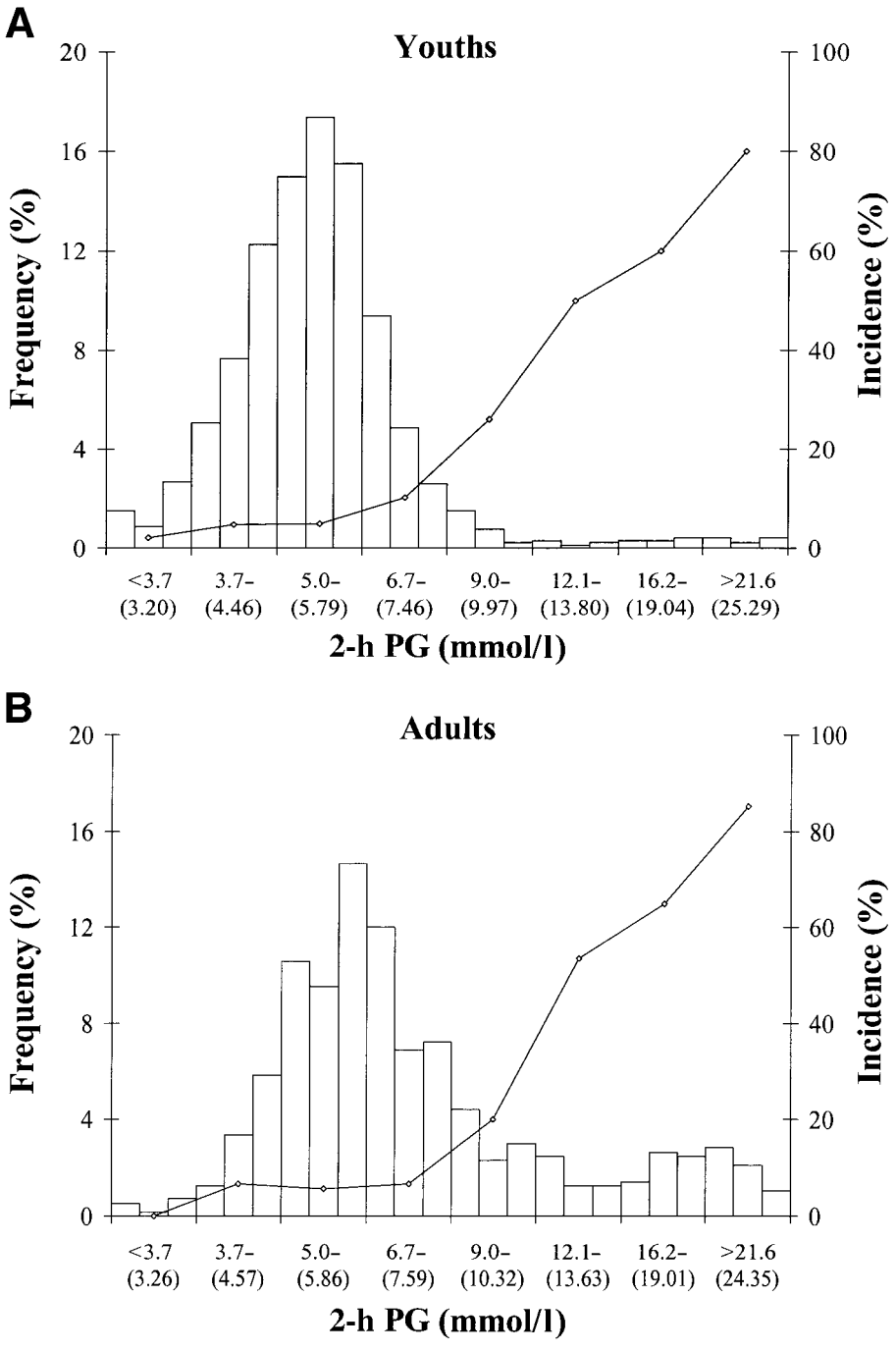

Figure 2—*Incidence of microvascular disease by 2-h PG for the youths* (A) *and adults* (B). *The* x*-axis represents 2-h PG on a log scale. The top numbers represent the boundaries for the glucose categories. The numbers in parenthesis represent the mean glucose for that category (e.g., glucose category 5.0–6.6 mmol/l, mean 5.59 mmol/l). The columns represent frequency distribution for 2-h PG for all subjects (left* y*-axis). The line represents incidence of microvascular disease within each glucose category (right* y*-axis)*

ication would eliminate only the most hyperglycemic subjects, we chose to include those subjects. Individuals were classified into categories based on glucose concentrations in relation to reference points that were equidistant on a logarithmic scale. Cumulative incidence of microvascular disease was taken as the proportion of subjects within each category who developed disease.

The differences in the predictive properties between the youths and adults were assessed by combining the groups in the logistic-regression model (using FPG and 2-h PG as continuous variables) and testing an interaction term.

The properties of specific levels of FPG and 2-h PG for predicting microvascular disease were determined by calculating sensitivity and specificity. Sensitivity was defined as the percentage of subjects with a microvascular endpoint whose baseline FPG or 2-h PG was greater than or equal to a specific cutoff. Specificity was defined as the percentage of subjects without a microvascular endpoint, whose baseline FPG or 2-h PG was below the cutoff. Receiver operating characteristics (ROC) curves were also generated for FPG and 2-h PG for each group.

ROC curves are plots of the sensitivity versus 1-specificity and are useful for determining the characteristics of a diagnostic test. The area under the ROC curve, which was calculated with the Wilcoxon statistic (19), quantifies the diagnostic accuracy of a test. ROC curve areas range from 0.5 to 1.0. An area of 0.5 implies no separation of the test values in the affected and unaffected groups. An area of 1.0 implies perfect separation between test values in the two groups. The area under the ROC curve indicates the strength of the association between the test variable and the outcome measure (19,20).

RESULTS — The youth group had 928 subjects, of whom 73 developed microvascular disease, and the adult group had 566 subjects, of whom 104 developed microvascular disease (Table 1). Median follow-up was slightly longer in the youth group.

Figures 1 and 2 show the frequency distributions of baseline FPG and 2-h PG on a log scale plotted with the incidence (percent) of microvascular disease. The frequency distributions for glucose clearly differ between the groups, with much higher percentages of individuals in the youth group (aged 5–19 years) in the lower glucose categories. For FPG (Fig. 1) and 2-h PG (Fig. 2), the incidence of microvascular disease began to increase dramatically at similar points in each age group. For FPG, the increase occurred at FPG 7.34 mmol/l in the youths and at 7.53 mmol/l in the adults; for 2-h PG, the increase occurred at 9.97 mmol/l (youths) and 10.32 mmol/l (adults). The sustained

Table 1—*Baseline characteristics for youths and adults*

	Youths	Adults
Baseline age (years)	15–19	20–34
n	928	566
Male	386 (41.6)	185 (32.7)
Female	542 (58.4)	381 (67.3)
Subjects who developed a microvascular endpoint (*n*)	73	104
Subjects who developed retinopathy and nephropathy (*n*)	16	32
Subjects who developed retinopathy only (*n*)	12	31
Subjects who developed nephropathy only (*n*)	45	41
Time to follow-up (years)	14.0 (5.2–24.6)	13.2 (5.7–27.0)

Data are *n* (%) and median (range), unless otherwise indicated.

increase in the percentage of subjects within these glucose groups who developed microvascular disease suggested an approximate threshold. Yet, the percentage of subjects developing microvascular disease who had baseline glucose concentrations above these apparent thresholds was very different in each group. In fact, among the subjects who developed microvascular disease, the percentage with baseline FPG ≥6.7 mmol/l or 2-h PG ≥9.0 mmol/l was twice as high in adults (64.4 and 76.0%, respectively) as in youths (23.2 and 31.5%, respectively). Therefore, in youths, only a minority of subjects who developed microvascular disease had relatively high (FPG ≥6.7 mmol/l and 2-h PG ≥9.0 mmol/l) baseline blood glucose.

When the age groups were combined in a logistic regression analysis including FPG, group (youth or adult), and an interaction term, there was no significant interaction, i.e., the slopes of the complication-FPG curves were not significantly different between age groups. Similarly, there was no significant interaction between group and 2-h PG. This suggested that a given difference in glucose values was associated with a similar increase in risk for development of microvascular disease in both groups. The absolute risk for development of complications was higher at each FPG and 2-h PG level for adults compared with youths, but not significantly. Odds ratios comparing adults to youths for the models containing FPG and 2-h PG were 1.3 ($P = 0.13$) and 1.1 ($P = 0.75$), respectively.

The diagnostic properties of FPG and 2-h PG are shown in Table 2. Sensitivity for FPG ≥7.0 mmol/l and 2-h PG ≥11.1 mmol/l was substantially lower for youths than for adults. Sensitivity improved at lower glucose thresholds (in this case FPG ≥5.9 mmol/l and 2-h PG ≥8.9 mmol/l) for youths without a substantial decrease in specificity, which was not the case for adults. Furthermore, ROC curve areas were lower for youths than for adults (Table 3), suggesting a weaker relationship between microvascular disease and baseline glucose. However, when nephropathy and retinopathy were analyzed separately, the area was lower for nephropathy but nearly equal for retinopathy in youths compared with adults.

CONCLUSIONS — The current guidelines for the diagnosis of diabetes are based on adult-population studies that have evaluated the relationship between glucose concentrations and microvascular disease (1). Because of the paucity of cases, similar information in youths has not been available. The ongoing biennial examinations of the Pima Indians have allowed us to collect follow-up data on a large number of individuals at various glucose levels during childhood and adolescence. We have shown that development of microvascular disease was related to levels of FPG and 2-h PG in youths. Results for the FPG were consistent with current ADA and WHO criteria; the results for the 2-h PG suggested a slightly lower diagnostic glucose level.

Based on these data, adult diagnostic guidelines for diabetes can be reasonably applied to youth. The similar slopes for FPG and 2-h PG in the logistic model suggest that youths are at increased risk of microvascular disease as glucose values increase, as in adults. However, our analysis suggested that the relationship between microvascular disease and glucose concentrations was different in youths than in adults. The ROC curve areas showed that microvascular disease was less well predicted by baseline glucose in youths than in adults. This difference between youths and adults is reflected in the low sensitivity in youths according to the 1997 ADA criteria and the difference in the percentage of complications defined by subjects with elevations in FPG and 2-h PG. The majority of the youths who developed microvascular disease still had glucose regulation in the impaired or normal ranges at baseline. Therefore, a large number of young at-risk subjects would not be identified by FPG or 2-h PG, unless "at-risk" was defined by a lower cutoff point or unless factors in addition to glucose were found to be of more or additive importance.

The differences between the two age groups in the predictive properties of glucose concentrations for subsequent microvascular disease may be largely caused by the differences in the frequency distributions of glucose at baseline (Figs. 1 and 2). The difference in the incidence of microvascular disease between the two groups at any given baseline glucose was modest. Therefore, in the younger subjects (youths), a greater percentage of those who developed microvascular disease may have come from the lower glucose categories simply because they made up a much larger percentage of the baseline population.

Another potential consequence of the differences in frequency distributions of glucose at baseline was that a greater proportion of younger individuals who developed microvascular disease developed proteinuria, a complication that may be less specific for hyperglycemia than reti-

Table 2—*Diagnostic characteristics for glucose*

	FPG		2-h PG	
	≥5.9	≥7.0	≥8.9	≥11.1
Youths				
Sensitivity*	31.2	23.0	32.8	23.0
Specificity†	94.3	98.6	96.3	98.4
Adults				
Sensitivity	78.1	63.0	76.7	68.5
Specificity	76.6	90.8	79.5	88.2

Data are %. *Percentage of subjects with microvascular disease whose baseline FPG or 2-h PG was greater than or equal to the specific glucose cutoff; †percentage of subjects without microvascular disease whose baseline FPG or 2-h PG was less than the specific glucose cutoff.

Table 3—*ROC curve areas*

	Microvascular disease*		Nephropathy†		Retinopathy‡	
	FPG	2-h PG	FPG	2-h PG	FPG	2-h PG
Youths	0.70 ± 0.04	0.71 ± 0.04	0.70 ± 0.04	0.70 ± 0.04	0.79 ± 0.05	0.84 ± 0.05
Adults	0.85 ± 0.02	0.84 ± 0.02	0.83 ± 0.03	0.83 ± 0.03	0.88 ± 0.03	0.86 ± 0.03

Data are areas ± SE. *Includes subjects who developed retinopathy, nephropathy, or both; †includes subjects who developed nephropathy with or without retinopathy; ‡includes subjects who developed retinopathy with or without nephropathy.

nopathy. In fact, when ROC curve analyses were conducted separately for each complication, retinopathy was as strongly related to glucose in youths as it was in adults, as demonstrated by the nearly equal ROC curve areas. The ROC curve area for nephropathy was lower in youths than in adults, suggesting that other factors specific for youth might be important in the development of nephropathy in this group. For instance, the hyperinsulinemia documented in young Pimas (21) might influence development of the kidney via interaction with the growth hormone axis (22–24).

In summary, despite the lower sensitivity for established diagnostic thresholds and the weaker association with microvascular disease, the incidence of microvascular disease increased at similar points in youths and adults in this population with a high prevalence of type 2 diabetes. In conclusion, it is reasonable to apply the adult diagnostic criteria for diabetes to children and adolescents.

Acknowledgments— We thank the members of the Gila River Indian Community for their continued support and participation and the staff of the Diabetes and Arthritis Epidemiology Section for help in this study.

References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
2. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*. Geneva, World Health Org., Department of Noncommunicable Disease Surveillance, 1999
3. McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 308: 1323–1328, 1994
4. Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, Badran A, Sous ES, Ali MA: Comparison of fasting and 2-h glucose and HbA_{1c} levels for diagnosing diabetes: diagnostic criteria and performance revisited. *Diabetes Care* 20:785–791, 1997
5. Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, Knowler WC: Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization Criteria for diagnosis of diabetes. *Diabetes Care* 23:1113–1118, 2000
6. Kitagawa T, Owada M, Urakami T, Tajima N: Epidemiology of type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in Japanese children. *Diabetes Res Clin Pract* 24 (Suppl.):S7–S13, 1994
7. Dabelea D, Hanson RL, Bennett PH, Roumain J, Knowler WC, Pettitt DJ: Increasing prevalence of type II diabetes in American Indian children. *Diabetologia* 41:904–910, 1998
8. Harris SB, Perkins BA, Whalen-Brough E: Non-insulin-dependent diabetes mellitus among First Nations children: new entity among First Nations people of north western Ontario. *Can Fam Physician* 42:869–876, 1996
9. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P: Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr* 128:608–615, 1996
10. Neufeld ND, Raffel LJ, Landon C, Chen YD, Vadheim CM: Early presentation of type 2 diabetes in Mexican-American youth. *Diabetes Care* 21:80–86, 1998
11. Rosenbloom AL, Joe JR, Young RS, Winter WE: Emerging epidemic of type 2 diabetes in youth. *Diabetes Care* 22:345–354, 1999
12. Knowler WC, Bennett PH, Bottazzo GF, Doniach D: Islet cell antibodies and diabetes mellitus in Pima Indians. *Diabetologia* 17:161–164, 1979
13. 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* 28:937–942, 1979
14. Katzeff HL, Savage PJ, Barclay-White B, Nagulesparan M, Bennett PH: C-peptide measurement in the differentiation of type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 28:264–268, 1985
15. Hanson RL, Ehm MG, Pettitt DJ, Prochazka M, Thompson DB, Faroud T, Kobes S, Baier L, Burns DK, Almasy L, Blangero J, Garvey WT, Bennett PH, Knowler WC: An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians. *Am J Hum Genet* 63:1130–1138, 1998
16. Baier LJ, Permana PA, Traurig M, Dobberfuhl A, Wiedrich C, Sutherland J, Thuillez P, Luczy-Bachman G, Hara M, Horikawa Y, Hinokio Y, Hanson RL, Bogardus C: Mutations in the genes for hepatocyte nuclear factor (HNF)-1α, -4α, -1β, and -3β; the dimerization cofactor of HNF-1; and insulin promoter factor 1 are not common causes of early-onset type 2 diabetes in Pima Indians. *Diabetes Care* 23:302–304, 2000
17. Dabelea D, Palmer JP, Bennett PH, Pettitt DJ, Knowler WC: Absence of glutamic acid decarboxylase antibodies in Pima Indian children with diabetes mellitus. *Diabetologia* 42:1265–1266, 1999
18. Shevky M, Stafford M: A clinical method for the estimation of protein in urine and other body fluids. *Arch Int Med* 32:222–225, 1923
19. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 143: 29–36, 1982
20. Zweig MH, Campbell G: Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 39:561–577, 1993
21. Pettitt DJ, Moll PP, Knowler WC, Mott DM, Neslon RG, Saad MF, Bennett PH, Kottke BA: Insulinemia in children at low and high risk of NIDDM. *Diabetes Care* 16:608–615, 1993
22. Attia N, Tamborlane WV, Heptulla R, Maggs D, Grozman A, Sherwin RS, Caprio S: The metabolic syndrome and insulin-like growth factor I regulation in adoles-

cent obesity. *J Clin Endocrinol Metab* 83: 1467–1471, 1998
23. Cummings EA, Sochett EB, Dekker MG, Lawson ML, Daneman D: Contribution of growth hormone and IGF-I to early diabetic nephropathy in type 1 diabetes. *Diabetes* 47:1341–1346, 1998
24. Lawson ML, Sochett EB, Chait PG, Balfe JW, Daneman D: Effect of puberty on markers of glomerular hypertrophy and hypertension in IDDM. *Diabetes* 45:51–55, 1996