An Explanation for the Increase in Heart Disease Mortality Rates in Diabetic Pima Indians

Effect of renal replacement therapy

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OBJECTIVE — Diabetic nephropathy (DN) became the leading cause of death in diabetic Pima Indians in the 1970s, but was superseded by ischemic heart disease (IHD) in the 1980s. This study tests the hypothesis that the rise in the IHD death rate between 1965 and 1998 is attributable to access to renal replacement therapy (RRT).

RESEARCH DESIGN AND METHODS — Underlying causes of death were determined among 2,095 diabetic Pima Indians ≥35 years old during four 8.5-year time intervals. To assess the effect of access to RRT on IHD death rates, trends were reexamined after subjects receiving RRT were classified as if they had died of DN.

RESULTS — During a median follow-up of 11.1 years (range 0.01–34), 818 subjects died. The age- and sex-adjusted DN death rate decreased over the 34-year study ($P = 0.05$), whereas the IHD death rate increased from 3.3 deaths/1,000 person-years (95% CI 1.4–5.2) to 6.3 deaths/1,000 person-years (95% CI 4.5–8.0; $P = 0.03$). After 151 subjects on RRT were reclassified as if they had died of DN, the death rate for DN increased from 4.8 deaths/1,000 person-years (95% CI 2.6–7) to 11.3 deaths/1,000 person-years (95% CI 9–13.6; $P = 0.0007$), whereas the increase in the IHD death rate disappeared ($P = 0.57$).

CONCLUSIONS — The incidence rate of renal failure attributable to diabetes has increased rapidly over the past 34 years in Pima Indians. IHD has emerged as the leading cause of death due largely to the availability of RRT and to changes in the pattern of death among those with DN.

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Diabetes is the leading cause of end-stage renal disease (ESRD) in the U.S., accounting for 43% of new cases (1). Rapid increases in the incidence rates of both diabetes and kidney failure attributable to diabetes have led to the prediction that diabetes may soon account for half of the new cases of ESRD in developed countries (2). Diabetic ESRD is also increasing rapidly in developing countries, where the public health infrastructure to care for this disease is limited (3). In the U.S. there is considerable racial/ethnic variability in the incidence rate of ESRD in diabetic populations, with much higher rates in American Indians, Hispanics, and African Americans than in non-Hispanic whites (3,4). The highest rates are found in American Indians, in whom the incidence of diabetes has risen dramatically over the past 50 years, probably as a consequence of dietary and lifestyle changes (5,6).

As recently as the 1970s, standard clinical practice in the U.S. typically excluded most persons with diabetes from dialysis and transplantation, in part because their poorer prognosis relative to other causes of ESRD made it difficult to justify expending limited resources on those with diabetes. Now, because of better control of diabetes, advances in the technology and delivery of renal replacement therapy (RRT), and widespread availability of federally funded RRT, criteria for initiation of RRT have changed so that diabetic patients make up the single largest group of RRT recipients. This change in clinical practice and in the availability of RRT may have altered the causes of death among diabetic patients, particularly in populations at high risk for diabetic kidney disease, since RRT permits those with diabetic ESRD to survive for long periods after the loss of kidney function.

In this study, we examined the impact of RRT on underlying causes of death from 1965 through 1998 in diabetic Pima Indians of the Gila River Indian Community, an American Indian population with an incidence rate of diabetic ESRD 14 times that of the U.S. diabetic population aged 45–64 years (7). RRT became available on a limited basis in the community in the 1970s and was widely available by the early 1980s. During this time interval ischemic heart disease emerged as the leading underlying cause of death among those with diabetes (8).

RESEARCH DESIGN AND METHODS

— Pima Indians and the closely related Tohono O'odham (Papago) Indians, who live in the Gila River Indian Community in the desert of central Arizona, participate in a comprehensive longitudinal diabetes study. Since 1965, each member of the population ≥5-years-old is invited to have a research examination approximately every 2 years. These biennial examinations include measurements of venous plasma glucose,

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Abbreviations: DN, diabetic nephropathy; ESRD, end-stage renal disease; IHD, ischemic heart disease; RRT, renal replacement therapy.

Table 1—*Number of deaths and death rates* for leading underlying causes, all natural and external causes, and all causes of death in diabetic Pima Indians in four time intervals from 1965 through 1998*

Underlying cause of death	ICD-9 codes	March 1965 to June 1973		July 1973 to December 1981		January 1982 to June 1990		July 1990 to December 1998		
		Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate	*P*
IHD	410.0–414.9	13	3.3	23	4.2	41	6.4	62	6.3	0.03
DN	250.4	20	4.8	36	6.1	35	4.2	34	3.6	0.05
Stroke	431.0–434.9; 436	6	2.1	12	1.9	12	1.3	16	2.0	0.90
Infections	See below†	26	7.3	24	4.2	25	3.4	45	5.0	0.04
Malignant neoplasms	140.0–208.9	7	2.0	17	2.9	29	4.3	30	3.2	0.29
Alcoholic liver disease	571.0–571.3	9	2.6	13	2.6	19	2.7	20	2.0	0.92
Other natural causes		32	9.4	28	5.5	40	6.8	56	6.9	0.07
All natural causes		113	31.6	153	27.4	201	29.1	263	28.9	0.59
All external causes		13	3.9	20	3.9	23	3.7	32	3.4	0.96
All causes		126	35.5	173	31.3	224	32.8	295	32.3	0.57

*Death rates are age- and sex-adjusted and reported per 1,000 person-years; †ICD-9 codes for infections: 001.0–139.8, 320.0–326.9, 460.0–466.1, 480.0–487.8, 540.0–543.9, 572.0, 590.0–590.9, 599.0, 680.0–686.9, and 729.4.

obtained 2 h after a 75-g oral glucose load, and an assessment of complications of diabetes. Diabetes is diagnosed by World Health Organization criteria (9), and the date of diagnosis is determined from the biennial examinations or from review of clinical records if diabetes is diagnosed between research examinations in the course of routine medical care.

The study population of 2,095 subjects included all persons with type 2 diabetes who resided in the community at any time between 1 January 1965 and 31 December 1998 and had one or more research examinations after 35 years of age. Each subject's vital status as of 31 December 1998 was determined. The underlying cause for the 818 deaths was determined by review of clinical records, reports of autopsy findings, and death certificates as described previously (10). Terminology and codes of the *International Classification of Disease, Ninth Revision* (ICD-9), were used to record underlying causes of death.

Statistical analysis

Death rates were calculated as the number of subjects who died per 1,000 person-years of follow-up. The period of risk extended from the date of the first biennial research examination after the age of 35 years in those with diabetes to death or 31 December 1998, whichever came earlier. Changes in death rates for diabetic nephropathy (DN) and ischemic heart disease (IHD) were examined during four 8.5-year time intervals (March 1965 through June 1973, July 1973 through December 1981, January 1982 through June 1990, and July 1990 through December 1998). Age-adjusted and age- and sex-adjusted death rates were calculated by direct standardization to the 1980 Pima Indian population. Tests for general association were computed by the Mantel-Haenszel test (11) adapted for person-year denominators (12) and for linear association by the Mantel extension test (13).

To assess the effect of access to RRT on underlying causes of death, trends were reexamined after the 151 subjects who were on RRT for at least 90 days were reclassified as if they had died of DN. Ninety days represents the median survival after the onset of kidney failure in the study subjects not receiving RRT. Subjects dying <90 days after the initiation of RRT were not reclassified. Median survival was ascertained by first determining the median serum creatinine concentration at the onset of RRT (6.9 mg/dl) in subjects who did receive RRT during the study, and then calculating the median survival from the date this creatinine value was reached in those dying without receiving RRT.

The risk of IHD death attributable to exposure to RRT, or the population-attributable risk, was computed as the difference in IHD death rates between the total population and those not receiving RRT divided by the IHD death rate in the total population (14). Because few sub-

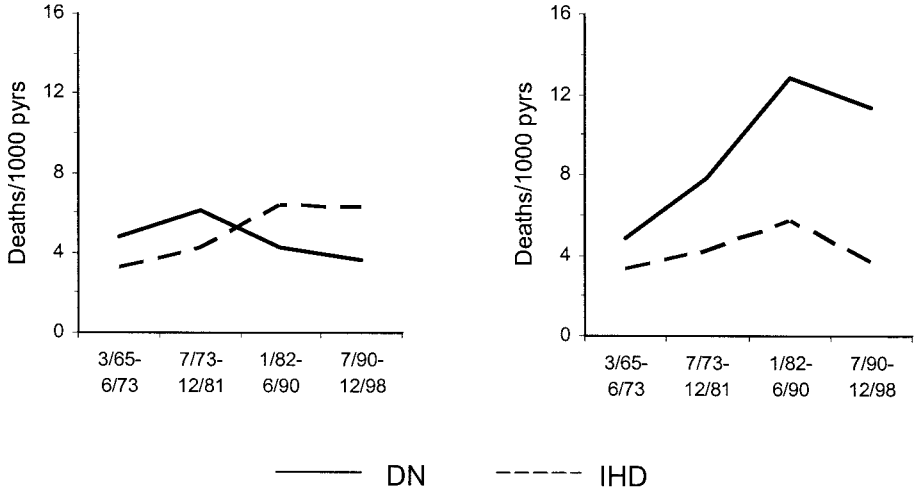

Figure 1—*Actual and reclassified age- and sex-adjusted death rates for DN and IHD in diabetic Pima Indians ≥35-years-old during the 34-year study.*

Table 2—*Number of deaths and death rates* for natural causes in diabetic Pima Indians in four time intervals from 1965 through 1998 according to the duration of diabetes*

	March 1965 to June 1973			July 1973 to December 1981			January 1982 to June 1990			July 1990 to December 1998		
	Deaths	Person-years	Rate	Deaths	Person-years	Rate	Deaths	Person-years	Rate	Deaths	Person-years	Rate
Duration of diabetes (years)												
≥10 years	67	2,545.5	25.9	35	2,879.4	16.4	25	2,869.5	17.0	20	3,451.3	10.5
10 years	46	861.5	54.9	118	2,685.8	38.0	176	4,626.1	35.2	243	6,250.0	34.7
Age (mean ± SD)	56.5 ± 13.8			56.0 ± 14.0			55.0 ± 14.0			54.0 ± 13.0		
Proportion (%) of total person-time in each period in subjects with 10 years' duration of diabetes	25			48			62			64		

*Death rates are age- and sex-adjusted and reported per 1,000 person-years.

jects received RRT in the first two study periods, the population-attributable risk for IHD in those with renal failure during these intervals was almost zero. Accordingly, the risk of IHD attributable to RRT by age-group within the population was computed for only the last two time intervals.

RESULTS — Of the 2,095 diabetic subjects (880 men and 1,215 women), all but 91 were American Indians, and 2,004 (96%) were at least 50% Pima, Tohono O'odham, or a mixture of these two closely related tribes. During a median follow-up of 11.1 years (range 0.01–34), 818 subjects died.

The age- and sex-adjusted death rate from all natural causes in diabetic Pima Indians was unchanged during the study ($P = 0.59$) (Table 1). The death rate from DN declined throughout the study ($P = 0.05$). On the other hand, the IHD death rate increased from 3.3 deaths/1,000 person-years (95% CI 1.4–5.2) in the first interval to 6.3 deaths/1,000 person-years (95% CI 4.5–8; $P = 0.03$) in the last interval; the death rate for IHD exceeded that for DN in the third and fourth intervals (Fig. 1). The proportion of IHD deaths attributable to RRT, i.e., the risk attributable to this exposure, was highest in subjects aged 35–54 years (64%) and declined with advanced age.

As shown in Table 2, death rates in diabetic Pima Indians were higher in those with longer duration of diabetes in each interval. Moreover, the proportion of person-time accumulated in the diabetes duration category ≥10 years increased with each successive time interval, reflecting an increase in the average duration of diabetes over time.

To determine the effect of RRT on overall and cause-specific mortality, subjects who received RRT for at least 90 days and whose deaths were not already attributed to DN were reclassified as dying from DN. Of the 151 subjects who were reclassified, 48 were alive and receiving RRT at the end of the study; the remaining 103 subjects who died during the study interval were reclassified as "diabetic nephropathy" from other underlying causes of death, including 37 from IHD and 23 from infectious diseases (Table 3). After reclassification, the age- and sex-adjusted death rate from all natural causes did not increase significantly ($P = 0.23$) (Table 4). Deaths from DN increased from 4.8 deaths/1,000 person-years (95% CI 2.6–7) to 11.3 deaths/1,000 person-years (95% CI 9–13.6; $P = 0.0007$), and the increase in the IHD death rate disappeared ($P = 0.57$) (Fig. 1).

Table 3—*Extent of reclassification of the underlying cause of death after reclassifying those receiving RRT as dying of DN*

Underlying cause of death*	Number of subjects reclassified to DN
IHD	37
Stroke	8
Infections†	23
Malignant neoplasms	2
Alcoholic liver disease	3
Other natural causes‡	21
External causes	9

*Forty-eight subjects who were alive and receiving RRT at the end of the study were also reclassified as dying of DN; †deaths from infectious diseases that were reclassified as DN included 15 parasitic infections, 6 influenza and pneumonias, and 2 skin infections; ‡includes 1 death from cardiovascular diseases other than IHD or stroke, 9 deaths from other diabetic causes, and 11 deaths from other natural causes.

Deaths from infectious diseases fluctuated widely during the study ($P = 0.04$), but the large increase in the death rate from infections in the last interval disappeared after reclassification, since 15 of the 45 deaths (33%) attributed to infectious diseases in this interval were reclassified as due to DN. The death rates for leading causes other than IHD and infections were largely unchanged after reclassification.

CONCLUSIONS — The emergence of IHD as a leading underlying cause of death in diabetic Pima Indians can be attributed largely to the availability of RRT and the resulting shift from DN to other underlying causes of death. Since DN and IHD share many of the same risk factors (15,16), substantial reductions in deaths from DN probably made a rise in IHD death rates inevitable. This finding suggests that a change in clinical practice, rather than a worsening of cardiovascular risk per se (17), is responsible for the current epidemic of IHD among diabetic patients in this population.

In the U.S., cardiovascular disease is the leading underlying cause of death among diabetic adults, and the Multinational Study of Vascular Disease in Diabetes (18) confirms the importance of IHD as the major cause of death in people

Table 4—*Number of deaths and death rates* for the six leading underlying causes, all natural and external causes, and all causes of death in diabetic Pima Indians in four time intervals from 1965 through 1998 after reclassifying those receiving RRT for at least 90 days as dying of DN*

Underlying cause of death	ICD-9 codes	March 1965 to June 1973		July 1973 to December 1981		January 1982 to June 1990		July 1990 to December 1998		
		Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate	*P*
IHD	410.0–414.9	13	3.3	23	4.2	35	5.7	31	3.7	0.57
DN	250.4	20	4.8	46	7.8	99	12.8	111	11.3	0.0007
Stroke	431.0–434.9; 436	6	2.1	11	1.8	11	1.3	10	1.6	0.70
Infections	See below†	26	7.3	20	3.6	21	2.9	30	3.6	0.006
Malignant neoplasms	140.0–208.9	7	2.0	17	2.9	29	4.4	28	3.1	0.26
Alcoholic liver disease	571.0–571.3	9	2.6	13	2.6	18	2.7	18	1.9	0.90
Other natural causes		32	9.4	28	5.5	36	6.3	39	5.7	0.03
All natural causes		113	31.6	158	28.5	249	36.0	267	30.9	0.23
All external causes		13	3.9	20	3.9	23	3.8	23	2.7	0.65
All causes		126	35.5	178	32.4	272	39.7	290	33.6	0.29

*Death rates are age- and sex-adjusted and reported per 1,000 person-years; †ICD-9 codes for infections: 001.0–139.8, 320.0–326.9, 460.0–466.1, 480.0–487.8, 540.0–543.9, 572.0, 590.0–590.9, 599.0, 680.0–686.9, and 729.4.

across the world with either type 1 or type 2 diabetes. Marked ethnic variation in cardiovascular risk among diabetic patients does occur, however, with lower IHD mortality in Asian populations from Japan and Hong Kong than in Caucasian populations elsewhere (18). Wide variations in IHD morbidity and mortality have also been reported among American Indian tribes, whose remote ancestry is Asian (19) but whose degree of admixture with other ethnic groups, especially Caucasians, is varied. The overall trend in IHD mortality in some American Indian tribes, as in the Pima Indians, is increasing (17,20), but the impact of RRT on this trend in other American Indian tribes or in other populations is not known. The increasing death rate from IHD in diabetic American Indians may contrast with that in the U.S. diabetic population. Data from the first National Health and Nutrition Examination Survey (NHANES I) (21) suggest that IHD mortality, at least in men, has declined modestly over the last 20 years. Furthermore, in the predominantly Caucasian population of Rochester, Minnesota, mortality rates among diabetic persons declined by almost 14% over a 25-year period, attributed largely to a reduction in cardiovascular deaths (22).

Periodic glucose tolerance testing permits the onset and duration of diabetes in Pima Indians to be estimated more precisely than in other populations. In the present study, the proportion of subjects with diabetes ≥10 years' duration increased in each successive time interval, which potentially contributed to a rise in death rates during the study and also to the continued rise in rates of DN despite improvements in plasma glucose and blood pressure control (23) and the introduction of inhibitors of the renin-angiotensin system. To ensure this trend did not reflect a systematic underestimation of diabetes duration in the early part of the study, the analysis was repeated in the subset of subjects ($n = 858$) who had a nondiabetic examination within 5 years of diabetes diagnosis. In this analysis, the average duration of diabetes also increased in successive time intervals (data not shown), indicating that the extent of underestimation, if present, was likely to be small. The use of 90 days as the cut point for reclassifying subjects on RRT as dying from DN does not account for changes in clinical practice over the study period. Nevertheless, the use of different cut points did not affect the conclusions of this study.

Infections are also a major cause of death among Pima Indians receiving RRT, accounting for 30 (25%) of the deaths in this group. Twenty-three of these deaths occurred after 90 days of RRT and were reclassified as deaths due to DN in our analysis. The major causes of death from infections included pneumonia (27%), disseminated coccidioidomycosis (27%), and sepsis (13%), reflecting the comorbid conditions and the immune dysfunction that characterizes uremia. In the U.S. general population, infectious diseases are the second leading cause of death among patients with ESRD, following cardiovascular disease (3). Sepsis accounts nationally for 75% of the infectious deaths, and pulmonary infections account for another 20% (3). Rate of hospitalizations for coccidioidomycosis and other fungal infections is also higher among dialysis patients in the U.S., particularly in those with diabetes (24).

In summary, the incidence rate of kidney failure attributable to diabetes has increased rapidly in the Pima Indians over the past three decades, and the introduction and widespread use of RRT in this population has prolonged many lives among those with diabetes (25). The initiation of RRT, however, has resulted in a rise in death rates due to displacing causes, particularly deaths from IHD and infectious diseases, and has led to the emergence of IHD as the leading cause of death in those with diabetes. The incidence of DN is high in populations such as the Pima Indians, in whom type 2 diabetes often occurs at young ages, and much of the fatal IHD develops in those with nephropathy. Therefore, prevention or delay of DN and the need for RRT may ultimately be the most effective way of preventing the increasing mortality rates from IHD in such populations.

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References

1. Minino AM, Smith BL: Deaths: preliminary data for 2000. *National Vital Statistics Report* 49 (Suppl. 12):1–40, 2001

2. National Diabetes Information Clearinghouse: *Kidney Disease of Diabetes*. Bethesda, MD, NIH, 1995 (publ. no. 97-3925)
3. U.S. Renal Data System: *USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD, NIH, NIDDK, 2003
4. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med* 321:1074–1079, 1989
5. Powers DR, Wallin JD: End-stage renal disease in specific ethnic and racial groups: risk factors and benefits of antihypertensive therapy. *Arch Intern Med* 158:793–800, 1998
6. Robbins DC, Knowler WC, Lee ET, Yeh J, Go OT, Welty T, Fabsitz R, Howard BV: Regional differences in albuminuria among American Indians: an epidemic of renal disease. *Kidney Int* 49:557–563, 1996
7. Nelson RG, Newman JM, Knowler WC, Sievers ML, Kunzelman CL, Pettitt DJ, Moffett CD, Teutsch SM, Bennett PH: Incidence of end-stage renal disease in type 2 (non-insulin-dependent) diabetes mellitus in Pima Indians. *Diabetologia* 31:730–736, 1998
8. Sievers ML, Nelson RG, Bennett PH: Sequential trends in overall and cause-specific mortality in diabetic and nondiabetic Pima Indians. *Diabetes Care* 19:107–111, 1996
9. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
10. Sievers ML, Nelson RG, Bennett PH: Adverse mortality experience of a southwestern American Indian community: overall death rates and underlying causes of death in Pima Indians. *J Clin Epidemiol* 43: 1231–1242, 1990
11. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22: 419–448, 1959
12. Rothman KJ, Boice JD: Follow-up (cohort) studies. In *Epidemiologic Analysis With a Programmable Calculator*. Washington, DC, NIH, 1979 (publ. no. 79-1649)
13. Mantel N: Chi-square tests with one degree of freedom: extension of the Mantel-Haenszel procedure. *J Am Stat Assoc* 59: 690–700, 1963
14. Last MJ: *A Dictionary of Epidemiology*. Oxford, U.K., Oxford University Press, 1988
15. Nelson RG, Pettitt DJ, Carraher MJ, Baird HR, Knowler WC: Effect of proteinuria on mortality in NIDDM. *Diabetes* 37:1499–1504, 1988
16. Nelson RG, Sievers ML, Knowler WC, Swinburn BA, Pettitt DJ, Saad MF, Liebow IM, Howard BV, Bennett PH: Low incidence of fatal coronary heart disease in Pima Indians despite high prevalence of non-insulin-dependent diabetes. *Circulation* 81:987–995, 1990
17. Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway JM, Go OT, Howard WJ, Rhoades ER, Robbins DC, Sievers ML, Welty TK: Rising tide of cardiovascular disease in American Indians: the Strong Heart Study. *Circulation* 99:2389–2395, 1999
18. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H: Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):14S–21S, 2001
19. Matson GA, Burch TA, Polesky HF, Swanson J, Sutton HE, Robinson A: Distribution of hereditary factors in the blood of Indians of the Gila River, Arizona. *Am J Phys Anthropol* 29:311–337, 1968
20. Klain M, Coulehan JL, Arena VC, Janett R: More frequent diagnosis of acute myocardial infarction among Navajo Indians. *Am J Public Health* 78:1351–1352, 1988
21. Gu K, Cowie CC, Harris MI: Diabetes and decline in heart disease mortality in US adults. *JAMA* 281:1291–1297, 1999
22. Thomas RJ, Palumbo PJ, Melton LJ 3rd, Roger VL, Ransom J, O'Brien PC, Leibson CL: Trends in the mortality burden associated with diabetes mellitus: a population-based study in Rochester, Minn, 1970–1994. *Arch Intern Med* 163:445–451, 2003
23. Nelson RG, Morgenstern H, Bennett PH: An epidemic of proteinuria in Pima Indians with type 2 diabetes mellitus. *Kidney Int* 54:2081–2088, 1998
24. Abbott KC, Hypolite I, Tveit DJ, Hshieh P, Cruess D, Agodoa LY: Hospitalizations for fungal infections after initiation of chronic dialysis in the United States. *Nephron* 89: 426–432, 2001
25. Nelson RG, Hanson RL, Pettitt DJ, Knower WC, Bennett PH: Survival during renal replacement therapy for diabetic end-stage renal disease in Pima Indians. *Diabetes Care* 19:1333–1337, 1996