Changes in BMI and Weight Before and After the Development of Type 2 Diabetes

HELEN C. LOOKER, MBBS[1]
WILLIAM C. KNOWLER, MD, DRPH[1]
ROBERT L. HANSON, MD, MPH[1]

OBJECTIVE — To examine weight changes occurring before and after the diagnosis of diabetes and the association of these changes with treatment and microvascular complications.

RESEARCH DESIGN AND METHODS — We undertook an analysis of serial examinations conducted between 1965 and 2000 in residents of the Gila River Community in Central Arizona. Data were taken from 4,226 examinations of 816 individuals in whom diabetes developed over the course of a longitudinal study and who had undergone a nondiabetic examination within 4 years preceding diagnosis. We measured changes in BMI between examinations.

RESULTS — Before diagnosis of diabetes, there were steady gains in weight: mean BMI climbed between 0.43 and 0.71 kg/m^2 per year. After diagnosis, the weight gain declined, and weight loss was generally seen; the mean rate of change of BMI ranged between −0.61 and +0.22 kg/m^2 per year. When current treatment was considered, there was greater weight stability in individuals taking insulin compared with those not taking hypoglycemic medication. Medication was a statistically significant factor for change in weight for most of the time intervals analyzed. There was no statistically significant association with retinopathy or nephropathy.

CONCLUSIONS — Before development of diabetes, there was a progressive rise in weight, and after diagnosis, there was a tendency toward weight loss. Weight-loss interventions in individuals with diabetes will need to account for this tendency if they are to successfully modify the course of the disease.

Diabetes Care 24:1917–1922, 2001

Obesity is a growing problem in the U.S.; 20% of men and 25% of women aged 20–74 years have a BMI ≥30 kg/m^2 (1). The prevalence of obesity is higher in populations such as the Pima Indians of Arizona, among whom >30% of men and >50% of women aged 20–64 years have a BMI ≥30 kg/m^2 (2). The link between high BMI and type 2 diabetes is well recognized (3–7). Because weight loss in individuals with diabetes results in short-term improvements in glycemic control (8), it has become a central strand of initial management of type 2 diabetes. However, good glycemic control is often achieved at the cost of weight gain (9). There are currently plans for a major clinical trial to compare interventions aimed at achieving weight loss in individuals with type 2 diabetes with conventional treatment of diabetes (10).

Few published data compare the natural history of weight changes after diagnosis of diabetes in individuals receiving standard medical care as opposed to individuals participating in a clinical trial. The purpose of this study was to examine data collected over the last 35 years in a longitudinal study of Pima Indians to describe changes in BMI in the time before and after diagnosis of diabetes. Diabetes is common among Pima Indians and is exclusively type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Data for this study are based on an ongoing population-based longitudinal study that has been taking place in the Gila River Indian Community in central Arizona since 1965. Community residents are invited to undergo examinations on a biennial basis beginning at 5 years of age, irrespective of health. These examinations include anthropometric measures, funduscopy, urinalysis, and measurement of plasma glucose levels. Diabetes was diagnosed by a 75-g oral glucose tolerance test according to World Health Organization guidelines (11) or the presence of a documented clinical diagnosis.

We included examinations of individuals in whom diabetes had developed during the course of the study. To improve accuracy on duration of diabetes, selection was limited to individuals who had undergone an examination within 4 years preceding diagnosis in which criteria for diabetes had not been met (a nondiabetic examination). Therefore, the maximum period of possible undiagnosed diabetes was 4 years. Examinations of pregnant women and individuals aged <15 years were excluded.

Weight and BMI were recorded at each examination, and changes and rate of change were calculated. Changes in BMI and weight were the differences in those values between consecutive examinations. Rate of change was the change divided by the time in years between examinations. These variables were plotted against time from diagnosis of diabetes, which was divided into 5-year intervals from 25 years before (−25 years) to >25 years after diagnosis. The intervals −5 to

From the [1]Diabetes and Arthritis Epidemiology Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona.

Address correspondence and reprint requests to Dr. H. Looker, Diabetes and Arthritis Epidemiology Section, NIDDK, 1550 East Indian School Rd., Phoenix, AZ 85014. E-mail: hlooker@mail.nih.gov.

Received for publication 9 May 2001 and accepted in revised form 7 August 2001.

Abbreviations:

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

Table 1—*Characteristics of participants by duration of diabetes in years*

Time from diagnosis (years)	No. of examinations (*n*)	Men	Age at examination (years)	Age at onset of diabetes <45 years	Mean BMI (kg/m^2)	Oral therapy	Insulin therapy*	Nephropathy	Retinopathy
−25 to −20	120	30.0	25.9 ± 9.0	46.7	29.4 ± 5.6	—	—	—	—
−20 to −15	169	31.4	29.3 ± 10.5	54.4	31.7 ± 6.7	—	—	—	—
−15 to −10	297	25.9	30.7 ± 12.3	62.0	32.0 ± 6.9	—	—	—	—
−10 to −5	452	30.5	33.2 ± 12.7	66.6	34.2 ± 6.9	—	—	—	—
−5 to −2	670	32.5	36.5 ± 13.6	69.6	36.1 ± 7.6	—	—	—	—
−2 to 0	311	35.7	37.8 ± 13.6	71.7	36.4 ± 7.6	—	—	—	—
0 to 2	672	33.6	40.5 ± 13.8	68.7	37.1 ± 8.0	8.6	1.3	2.1	1.7
2 to 5	516	31.8	42.9 ± 13.2	69.8	35.8 ± 8.0	22.7	7.8	2.9	0.8
5 to 10	422	32.0	46.3 ± 12.3	70.4	33.9 ± 7.3	33.0	15.3	2.9	5.6
10 to 15	277	30.0	51.3 ± 11.6	70.4	32.4 ± 6.8	31.0	28.2	12.2	24.3
15 to 20	194	29.4	54.3 ± 10.1	76.3	31.3 ± 6.9	37.8	33.9	29.6	41.9
20 to 25	93	30.1	58.6 ± 9.2	77.4	30.3 ± 7.0	26.3	52.6	46.2	51.9

Data are *n*, %, and means ± SD. All percentages are expressed as a percentage of examinations excluding missing data. Data on medication were available for 4,005 examinations (94.7% of all) and on retinopathy for 4,088 examinations (96.7% of all) and on nephropathy for 4,134 examinations (97.8% of all). The mean period of follow-up from first exam to last exam was 18.5 years (SD = 8.3) with a range of 1.7–34.6 years. There was a mean period before diagnosis of 9.6 years (SD = 7.2) and a mean period after diagnosis of 8.9 years (7.8). A total of 32 exams were excluded: 4 reported oral hypoglycemic treatment in the absence of diabetes, 10 reported retinopathy in the absence of diabetes, and 18 reported nephropathy in the absence of diabetes *People taking insulin with oral therapies were included in the insulin group.

+5 years were further subdivided for a more detailed picture of changes occurring around the time of diagnosis. To avoid undue influence of individuals who attended multiple examinations, only a single examination was used for an individual in a given time period. In individuals who had been examined more than once, the examination closest to the midpoint of the interval was selected. Similar trends were seen for all measures of weight change. We report rate of change of BMI for illustration.

The group was subdivided into those currently receiving (within 72 h before examination) either oral therapy, insulin therapy, or no hypoglycemic medication. Classification was based on treatment at the time of the current examination.

We looked for association between microvascular complications and changes in weight and BMI. Retinopathy was defined as the presence of microaneurysms alone or with exudates, retinitis proliferans, preretinal or vitreous hemorrhages, or any combination of these in at least one eye as noted on funduscopy after pupil dilation. Nephropathy was defined by a protein:creatinine ratio of a spot urine sample of ≥1 g/g. This is equivalent to excretion of ≥1 g of protein per 24 h (12). Retinopathy and nephropathy are rare among Pima Indians without diabetes; therefore, analyses of these complications were restricted to examinations after the diagnosis of diabetes (Table 1).

The group was also divided by age at diagnosis of diabetes using 45 years as a cutoff between early and late onset. Previous studies have shown a weaker relationship between BMI and diabetes in those with older age at onset (2).

In statistical analyses, the paired Student's *t* test was used to determine, in each time interval, whether the change in BMI (gain/loss) was significantly different from 0. Analysis of variance (*F* test) was used to compare these changes among groups determined by medication, age at onset, retinopathy, and nephropathy at each duration period. A *P* value <0.05 was considered statistically significant. We have used the general pattern of these results to describe factors associated with weight change, and therefore, we have not corrected *P* values for multiple comparisons. Similar conclusions were derived from analyses of all examinations simultaneously, using an autoregressive approach that models BMI as a function of BMI at the previous examination, the time between examinations, and covariates of interest (13,14).

RESULTS — After restriction of the study to individuals who had undergone a nondiabetic examination within 4 years preceding diagnosis, data were available from 5,754 examinations of 816 individuals. When limited to one examination per individual per time period, there were 4,226 examinations.

Mean BMI

The relationship between BMI and time from diagnosis resembled an inverted V with a positive association before diagnosis of diabetes, such that the highest BMI generally occurred at or immediately after diagnosis (0–2 years) (Table 1). Subsequently, increasing duration of diabetes was associated with progressively lower BMI.

Age at onset

The curve for those with early onset diabetes was again an inverted V. For those with late-onset diabetes, the relationship was flatter before diagnosis, but increasing duration of diabetes was again associated with lower BMI (Fig. 1*A*).

To determine whether individuals follow the pattern suggested by the population analysis, we selected groups of individuals who had undergone three to four examinations in consecutive duration periods and plotted the mean BMI against duration. The pattern was consistent with the cross-sectional data (Fig. 1*B*).

Intra-individual changes in BMI

For the whole group, there was a statistically significant increase in BMI in all periods before diagnosis of diabetes. In the period immediately after diagnosis, the increase became smaller but was still statistically significantly greater than 0. For most subsequent periods, there was a sta-

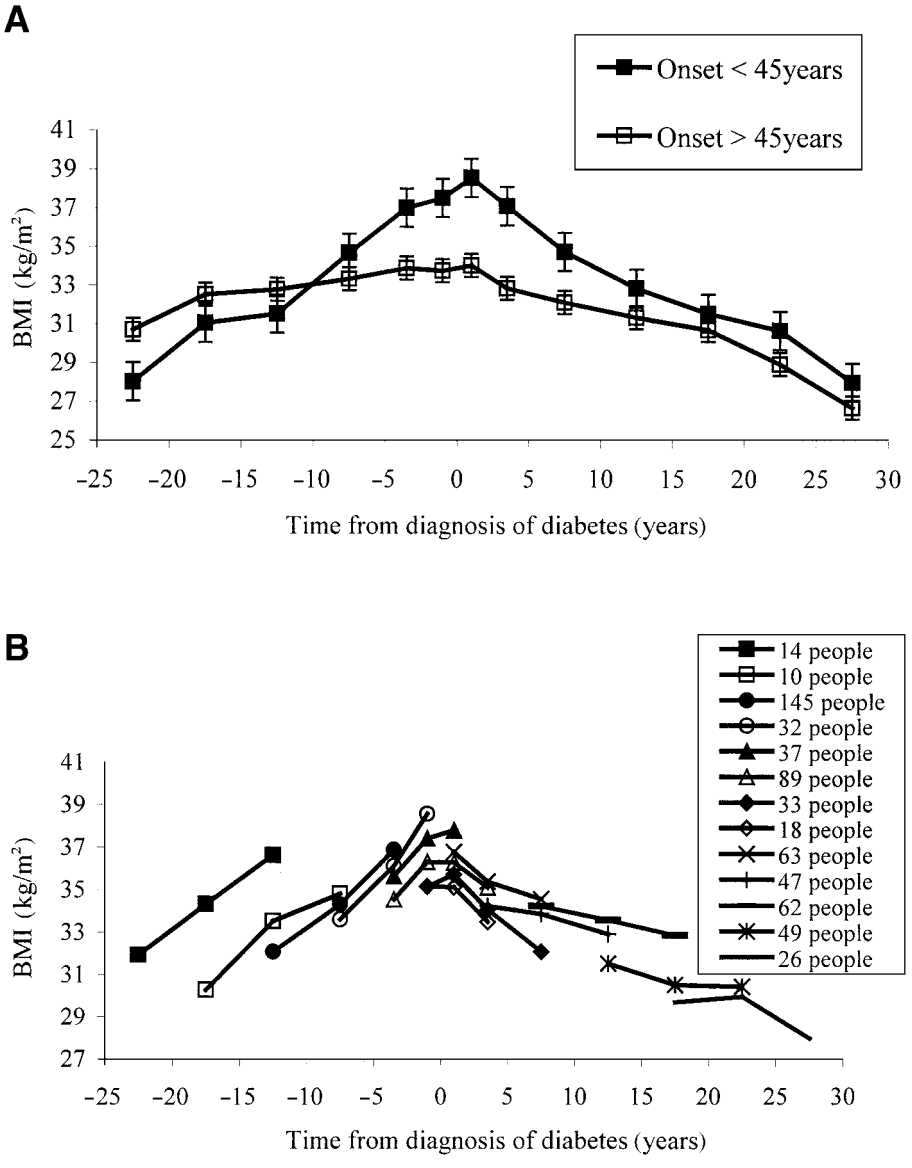

Figure 1—*BMI against time from diagnosis of diabetes by age at diagnosis.* A*: Cross-sectional data. The average age of onset for individuals with early onset diabetes was 32.4 years and for individuals with late-onset diabetes was 56.1 years. Error bars show standard error.* B*: Longitudinal data for all connected points. A total of 1,997 examinations were included in this analysis. Any one individual is included only once in any set of overlapping data.*

tistically significant decrease in BMI (Fig. 2*A*). When expressed as a percentage of previous BMI, the pattern was unchanged (Fig. 2*B*).

Age at onset

Intra-individual changes in BMI differed by age at onset of diabetes. Before diagnosis, the early onset group gained 0.5–1 kg/m^2 per year, whereas the late-onset group gained <0.5 kg/m^2 per year. After diagnosis, the rate of change in BMI was similar in both groups. For most time points, the individual differences in both groups were significantly different from 0. The two groups showed statistically significantly different degrees of change in most periods before diagnosis but in few periods after diagnosis.

BMI tended to increase in the population over time (2). To ensure this was not confounding our findings, we divided the group into those diagnosed before or after 1 January 1985. Mean BMI was higher at all duration periods for those diagnosed after 1 January 1985, but the intra-individual changes were similar for both groups. Analysis of variance showed that the groups differed significantly in rate of change of BMI only at time periods −5 to −2 years and 0–2 years, when those diagnosed after 1 January 1985 showed greater gains.

Sex

Although mean BMI was consistently higher in women than men, the rate of change in BMI was similar for both sexes and generally did not differ significantly. When comparing parous and nulliparous women, we found that mean BMI was higher at each duration period for the nulliparous women, significantly so between −10 and +5 years and 10–20 years. Rate of change of BMI, however, was similar between nulliparous and parous women, except around the time of diagnosis of diabetes, when nulliparous women had significantly greater weight gains. There were no significant differences in rate of change of BMI between premenopausal and postmenopausal women.

Diabetes medication

Individuals who were not taking antidiabetic medication tended to continue to lose weight after onset of diabetes. Insulin therapy was associated with greater weight loss at short durations of diabetes but with less weight loss or even weight gain at durations of diabetes >5 years. In individuals on oral antidiabetic therapy, the change in BMI was intermediate between the values of those taking insulin and those taking no medication. After 10 years of diabetes, individuals taking no medication always had a greater degree of decrease in BMI than those taking any medication (Fig. 3).

Glycemic control was assessed using fasting and 2-h blood glucose and HbA_{1c}. Analysis showed that the group taking no antidiabetic medication had lower values of all measures than the groups treated with oral therapy or insulin during all duration periods.

Retinopathy

Retinopathy was not associated with any clear change in pattern of rate of change of BMI. Analysis of variance performed for each duration period showed a statistically significant association between retinopathy and rate of change in BMI only in the period of 10–15 years, when those with retinopathy had less weight loss than

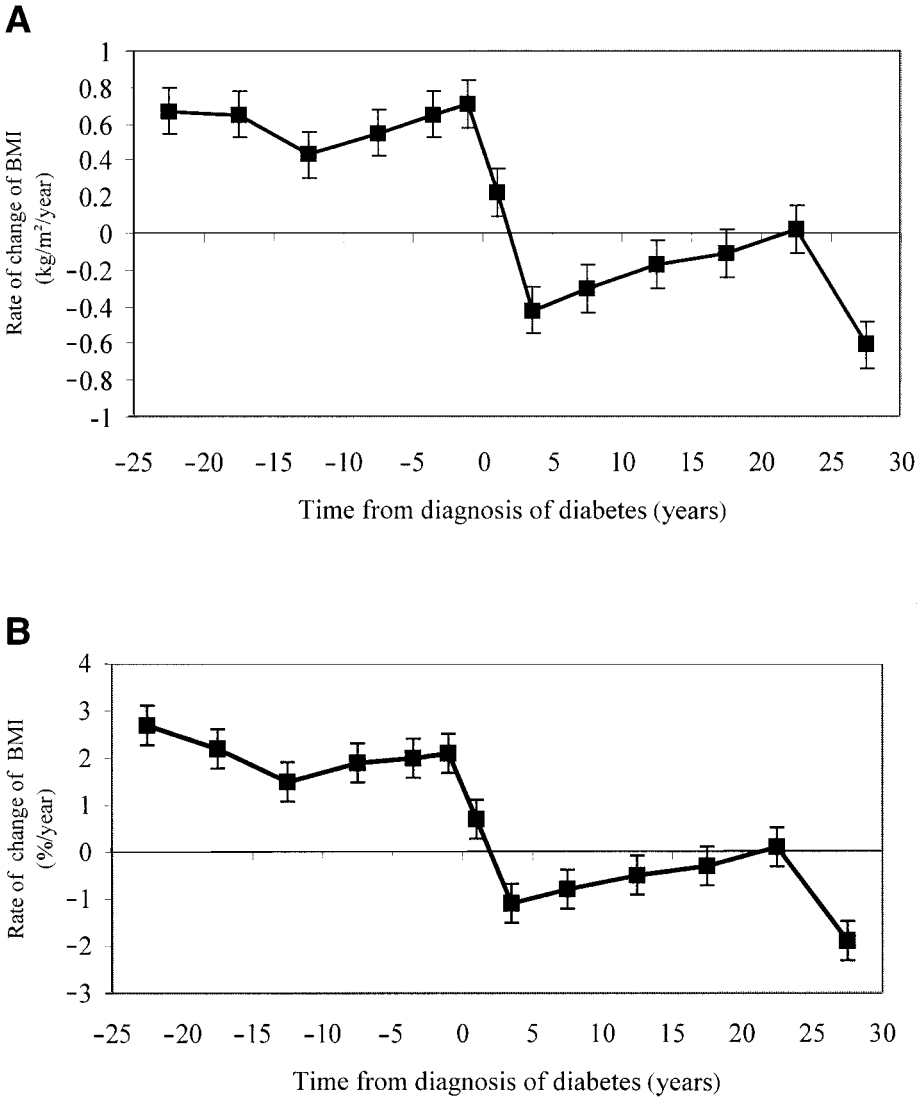

Figure 2—*Rate of change in BMI against time from diagnosis of diabetes.* A*: Change in BMI per year. All points are significantly different from 0, except between 20 and 25 years* ($P < 0.05$). B*: Percentage change in BMI per year. All points are significantly different from 0, except between 20 and 25 years* ($P < 0.05$).

those without retinopathy. When medication was included in the model, there was no statistically significant effect of retinopathy in any duration period, but significant effects of medication use remained when controlled for retinopathy.

Nephropathy

Within the first 5 years of diagnosis, there was a tendency for those with nephropathy to have a greater decrease in BMI than those without nephropathy. However, between 10 and 25 years after diagnosis, the decrease in BMI was less for individuals with nephropathy. Analysis of variance at each duration interval indicated a statistically significant difference in rate of change of BMI between the groups at durations 10–15 and 20–25 years, when the nephropathy group had less weight loss than the group without nephropathy. When medication was included in the model, there was no statistically significant effect of nephropathy in any duration period, but significant effects of medication use remained when controlled for nephropathy.

CONCLUSIONS — Obesity contributes to the development of type 2 diabetes, and weight control efforts are an important component of the clinical management of diabetes. Although epidemiological studies have examined weight change as a predictor of diabetes and intervention studies have shown that weight loss produces short-term improvements in glycemic control in people with type 2 diabetes, few data exist on how weight changes longitudinally in relation to the development of diabetes. The present analyses show that Pima Indians in whom diabetes developed tend to gain weight until diabetes is diagnosed and progressively lose weight afterward. This pattern of weight gain followed by weight loss has been previously described in this population over a relatively short period of time around the onset of diabetes (2,3). The present analyses extend those observations and demonstrate that this pattern persists over much longer periods of time, up to 25 years before and after the diagnosis of diabetes. The determination that mean BMI is higher in nulliparous women than in parous women has been observed previously in this population (15), although we found that rate of change in BMI generally was not affected by gravidity. Increasing age at diagnosis did not affect the rate of change in BMI after diagnosis of diabetes. Pharmacological treatment for hyperglycemia was associated with the rate of weight change. Individuals not treated with pharmacological agents tended to lose weight most rapidly and individuals treated with insulin lost weight least rapidly or even gained weight, whereas those treated with oral hypoglycemic agents had an intermediate weight loss. The presence of retinopathy or nephropathy was not associated with weight change.

The tendency for BMI to increase before diagnosis of diabetes is consistent with epidemiological studies showing that high BMI and weight gain predict incidence of diabetes (5,6,8,16), although links to weight loss have also been reported (17). Obesity in early adulthood has been positively linked with subsequent diabetes (4,5). In the Pima Indians, duration of obesity also increases the risk of developing diabetes (16).

A report from another American Indian population showed that over a 4-year period, there was an average individual weight loss of 3.7 kg in a group on various medical therapies for diabetes (18). In Irish people with symptomatic, newly diagnosed type 2 diabetes, most individuals underwent weight loss that was

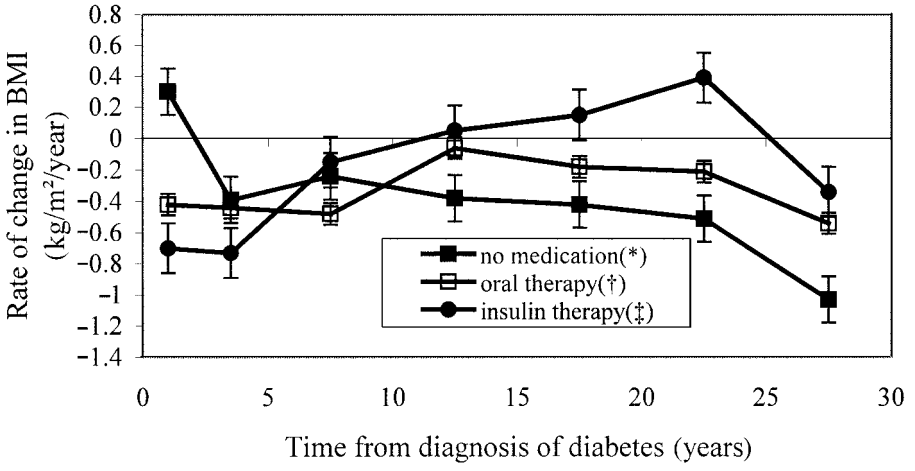

Figure 3—*Rate of change in BMI against time from diagnosis by treatment. Error bars show standard error. *All points are significantly different from 0 (*$P < 0.05$*); †points significantly different from 0 at 0–10 years and 15–20 years (*$P < 0.05$*); ‡points significantly different from 0 at 2–5 years and 20–25 years (*$P < 0.05$*).*

sustained for 10 years of follow-up (19). Individuals on oral hypoglycemic therapy showed less marked weight loss than those treated with diet alone. In a U.S. population study, weight loss was more likely to occur in those with diabetes than in those without (20). The most extensive clinical trial to study changes in weight was the U.K. Prospective Diabetes Study. They examined weight changes for various intention-to-treat groups. Over 10 years of follow-up, people in all treatment groups generally gained weight. Weight gain was most pronounced in those on intensive therapy with sulfonylureas or insulin (21). It is possible that the effects of dietary management on BMI were not seen fully, because those who achieved fasting blood glucose <6 mmol/l after the 3-month run-in period were excluded. There were many differences between the population examined in our study and that in U.K. Prospective Diabetes Study, including ethnicity, gender mix, baseline BMI, and, in our study, inclusion of all subjects regardless of initial glycemic control.

Type 2 diabetes often has an insidious onset, making it difficult for studies to assess how weight changes with respect to duration of diabetes. By contrast, because of systematic testing for diabetes in the Pima Indians, we were able to minimize the effects of undiagnosed disease by including only those who had undergone a nondiabetic examination within the 4 years preceding diagnosis. However, we were not able to determine whether weight loss was voluntary, for example in response to medically prescribed dietary therapy, or involuntary, perhaps due to catabolic effects of severe hyperglycemia. Glucose and HbA_{1c} levels indicate that the group treated with diet only achieved the best glycemic control. This suggests that they are primarily treated with diet alone by intention and that, not surprisingly, pharmacologic therapy is given to patients in whom hyperglycemia is harder to control. The fact that the individuals treated with insulin had greater weight gain despite worse glycemic control is consistent with the hypothesis that insulin causes weight gain.

We have considered oral therapy as a single group and did not subdivide by drug class. The biguanides may have different effects on BMI than the sulfonylureas and are often considered separately (22). However, metformin has only recently been introduced in the U.S. and was reported in too few examinations for separate analyses.

Most studies of BMI and complications have considered BMI as a predictor of the development of complications and have not looked at relationships with changes in BMI. Retinopathy has been associated with lower BMI in many (23,24) but not all (25) populations. An association with higher BMI and nephropathy has been reported (25), but others found no association (23).

The number of people with complications was small, which may be due, in part, to the short undiagnosed period of diabetes among those included. The power to differentiate an association with complications was, therefore, limited. Repeating the analysis with all individuals, regardless of potential duration of undiagnosed diabetes, gave similar results (data not shown). For nephropathy, it could be that weight is not affected until renal function declines further and that those with nephropathy advanced enough to cause weight loss constitute a small proportion of the study subjects.

Weight loss seems to be a desirable goal for most individuals in this population with a high mean BMI, because glycemic control, hyperlipidemia, and hypertension are all improved with weight loss in the short term (8,26). Concern has arisen because some epidemiological studies have linked weight loss with increased mortality. In the Pima Indian population, a U-shaped relationship has been described between BMI and mortality; the lowest mortality is associated with BMI between 30 and 35 kg/m^2. Weight loss was associated with increased mortality, although it could not be determined whether this weight loss was intentional (27). Williamson et al. found that self-reported intentional weight loss in overweight individuals with diabetes was associated with a reduced mortality rate (28).

In Pima Indians with diabetes, there is a tendency to lose weight such that BMI declines at a rate of 0.4–0.6 kg/m^2 per year (1–1.8% per year) after the onset of diabetes in individuals who are not taking antidiabetic medication. Medication was associated with different patterns of change in BMI, in keeping with the evidence that both sulfonylureas and insulin tend to stabilize weight. The presence or absence of microvascular complications has little association with changes in BMI. It is likely that weight loss interventions will need to achieve a greater degree of weight loss than observed here if they are to effectively modify the course of diabetes.

Acknowledgments— We thank the members of the Gila River Indian community and all the staff at the National Institutes of Health clinic in Sacaton. We also thank Dr. Antonio Tataranni for his advice and comments during the preparation of this manuscript.

References

1. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL: Overweight and obesity in the United States: prevalence and trends. *Int J Obes Relat Metab Disord* 22:39–47, 1998
2. Knowler WC, Pettitt DJ, Saad MF, Charles MA, Nelson RG, Howard BV, Bogardus C, Bennett PH: Obesity in the Pima Indians: its magnitude and relationship with diabetes. *Am J Clin Nutr* 53 (Suppl. 6): 1543S–1551S, 1991
3. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH: Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. *Am J Epidemiol* 113:144–156, 1981
4. Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, Speizer FE: Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 132:501–513, 1990
5. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961–969, 1994
6. Hanson RL, Narayan KM, McCance DR, Pettit DJ, Jacobsson LT, Bennett PH, Knowler WC: Rate of weight gain, weight fluctuation, and incidence of NIDDM. *Diabetes* 44:261–266, 1995
7. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF: Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* 46:701–710, 1997
8. Heilbronn LH, Noakes M, Clifton PM: Effect of energy restriction, weight loss, and diet composition on plasma lipids and glucose in patients with type 2 diabetes. *Diabetes Care* 22:889–895, 1999
9. U.K. Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
10. *Study of Health Outcome of Weight Loss (SHOW)*. [article online], 1998. Available from http://grants.nih.gov/grants/guide.rfa-files/RFA-DK-98.019.html. Accessed 18 November 1998
11. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
12. Ginsberg JM, Chang BS, Matarese RA, Garella S: Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med* 309:1543–1546, 1983
13. Rosner B, Munoz A: Autoregressive modeling for the analysis of longitudinal data with unequally spaced examinations. *Stat Med* 7:59–71, 1988
14. Rosner B, Munoz A: Conditional linear models for longitudinal data. In: *Statistical Models for Longitudinal Studies of Health*. Dwyer JH, Feinleib M, Lipport P, Hoffmeister H, Eds. Oxford, Oxford University Press, 1991, p. 115–131
15. Charles MA, Pettitt DJ, McCance DR, Hanson RL, Bennett PH, Knowler WC: Gravidity, obesity and non-insulin-dependent diabetes among Pima Indian women. *Am J Med* 97:250–255, 1994
16. Everhart JE, Pettitt DJ, Bennett PH, Knowler WC: Duration of obesity increases the incidence of NIDDM. *Diabetes* 41:235–240, 1992
17. Ford ES, Williamson DF, Liu S: Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol* 146:214–222, 1997
18. Newman WP, Hollevoet JJ, Frohlich KL: The diabetes project at Fort Totten, North Dakota, 1984–1988. *Diabetes Care* 16: 361–363, 1993
19. Hadden DR, Blair ALT, Wilson EA, McBoyle D, Atkinson AB, Kennedy AL, Buchanan KD, Merrett JD, Montgomery DA, Weaver JA: Natural history of diabetes presenting age 40–69 years: a prospective study of the influence of intensive dietary therapy. *Q J Med* 59:579–598, 1986
20. Mayer-Davis EJ, Karter AJ, Zaccaro DJ: Diabetes status, not insulin resistance, predicts weight loss in a tri-ethnic population. *Diabetes* 49 (Suppl. 1):185–186, 2000
21. U.K. Prospective Diabetes Study (UKPDS) Group: UKPDS 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ* 310:83–88, 1995
22. U.K. Prospective Diabetes Study (UKPDS) Group: Effect: of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
23. Klein R, Klein BE, Moss SE: Is obesity related to microvascular and macrovascular complications in diabetes? The Wisconsin study of diabetic retinopathy. *Arch Intern Med* 157:650–656, 1997
24. Nagi DK, Pettitt DJ, Bennett PH, Klein R, Knowler WC: Diabetic retinopathy assessed by fundus photography in Pima Indians with impaired glucose tolerance and NIDDM. *Diabet Med* 14:449–456, 1997
25. Haupt E, Benecke A, Haupt A, Herrmann R, Vogel H, Walter C: The KID study VI: diabetic complications and associated diseases in younger type 2 diabetics still performing a profession: prevalence and correlation with duration of diabetic state, BMI and C-peptide. *Exp Clin Endocrinol Diabetes* 107:435–441, 1999
26. Redmon JB, Raatz SK, Kwong CA, Swanson JE, Thomas W, Bantle JP: Pharmacologic induction of weight loss to treat type 2 diabetes. *Diabetes Care* 22:896–903, 1999
27. Hanson RL, McCance DR, Jacobsson LT, Narayan KM, Nelson RG, Pettitt DJ, Bennett PH, Knowler WC: The U-shaped association between body mass index and mortality: relationship with weight gain in a Native American population. *J Clin Epidemiol* 48:903–916, 1995
28. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T: Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care* 23:1499–1504, 2000