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

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

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/m² 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/m² 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.

From the 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.

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Abbreviations:
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—Characteristics of participants by duration of diabetes in years

| Time from diagnosis (years) | No. of examinations (n) | Age at examination Mean BMI Oral therapy Nephropathy Retinopathy <45 years (kg/m²) therapy* | | |
|-----------------------------|------------------------|-----------------------------------------|-----------------|-----------------|-----------------|-----------------|
| -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. 1A).

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. 1B).

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

**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/m² per year, whereas the late-onset group gained <0.5 kg/m² 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 HbA1c. 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
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
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 HbA1c 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/m². 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/m² 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.

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