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EPIDEMIOLOGY, OBESITY, AND NON-INSULIN-DEPENDENT DIABETES MELLITUS

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"While there is little doubt that obesity is in some way associated with both the prevalence and subsequent incidence of non-insulin-dependent diabetes, its exact role and its interaction with other factors have remained somewhat elusive" (1, p. 982).

Epidemiologic studies of obesity and diabetes, one of the oldest known chronic condition associations in medicine, antedated studies of obesity and cancer or heart disease. Joslin (2) was among the first to draw attention to the association between obesity and diabetes in a manner that would be acceptable to modern epidemiologists. In 1921, he described a study of weight and height in 1,000 diabetics compared by age with insured lives. He understood the importance of using consecutive cases and large samples, of actually measuring both height and weight, of giving some variation around the "normal standard" of the life insurance tables, of considering the degree of leanness as well as overweight, and the importance of the basic concept of risk ratios. Describing his data, Joslin wrote, "The table as a whole shows that of the 1,000 diabetics considered, the maximum weights of only 10 per cent were below the standard weight zone, while 15 per cent came in that zone and 75 per cent above it" (2, p. 81).

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In 1935, Himsworth (3) applied another classic epidemiologic method, time trends, to the study of diabetes. During World War I, countries with severe rationing had reduced diabetic mortality, while those whose food supplies were less affected showed no change. These data have been variously interpreted as the reduction in diabetes mortality in countries with severe rationing which resulted in consumption of more carbohydrate or fiber or in consumption of less fat or calories.

Other time-honored epidemiologic methods, including cross-cultural studies, studies of different ethnic groups within the same country, and migration studies, have supported an obesity-diabetes association. Landmark studies by Cohen (4) showing the increased prevalence of diabetes in Yemenite Jews living in Israel, by Prior and Davidson (5) comparing diabetes prevalence in Polynesians and Caucasians in New Zealand, and by West and Kalbfleisch (6) in 11 countries showing a strong and consistent association between the prevalence of diabetes and the mean body weight of that country's population were forerunners of the ongoing multinational studies, such as those by Zimmet et al. (7) in Pacific populations.

Despite this auspicious beginning, until 10 years ago there were very few population-based prospective studies of diabetes. Many were derivative of studies of the epidemiology of heart disease and suffered problems of definition and ascertainment bias. For example, a pioneering cohort study of 13,000 male executives showing relative weight to be a predictor of diabetes was based on known cases; one cannot exclude the probability that obese employees were more often tested for diabetes by a

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physician (8). In a 1972 report on cholesterol and heart disease, Westlund and Nicolaysen (9) noted an exponential association of relative weight and the incidence of diabetes in 3,751 Oslo men aged 40–49 years. Diabetes was not seen in those who weighed 10 per cent less than standard weight, rates of diabetes gradually rose with heavier body weights, and among those with gross obesity (45 per cent or more of standard weight), more than 12 per cent developed diabetes over a 10-year period. This widely quoted association was based on only 44 new cases ascertained from industrial physician records and was, therefore, again subject to ascertainment bias; i.e., a diagnosis of diabetes was sought more often in overweight men.

Cohort studies using population screening by standardized diagnostic criteria, with the potential to explore further the obesity-diabetes association, have only recently been attempted. A number of good questions, best addressed by epidemiologists, remain unanswered. Some, indeed, remain unasked.

What best characterizes the obesity-diabetes connection?

Several important questions related to obesity as a precursor of non-insulin-dependent diabetes include the following: Is there a threshold effect? What is the contribution of current versus prior weight? Of childhood versus adult-onset overweight? Of diet to maintain weight versus "naturally" lean? Of maximum overweight versus duration of overweight? Just how important is the distribution of body fat?

The threshold question, posed by West, has major public health implications: "At what level of fatness does increased susceptibility to diabetes begin?" (10, p. 243). On the basis of a prospective study in Israel, Modan et al. (11) found an exponentially increasing risk of diabetes diagnosed by oral glucose tolerance testing of 2,140 Israelis aged 40–70 years with increasing body mass index (based on weight and height measured 10 years earlier). High concurrent and high past body mass indices were similarly associated with impaired glucose tolerance, but only past obesity was predictive of non-insulin-dependent diabetes mellitus. Weight loss had no effect on the risk of subsequent diabetes. In those with stable body weights over 10 years, there was a linear increase in risk of impaired glucose tolerance with progressively higher weights, but an apparent threshold of risk for diabetes. The risk was so low at lower weight indices, however, that it was difficult to ascertain the role of relative leanness. An ideal weight, below which there is little or no risk, could reflect the instability of risk estimates at the lower level of risk.

When diabetes is very common, as in the Pima population, a continuous risk with increasing weight is seen (12). However, the average body mass index in Pima men and women exceeds both the average US body mass index and the current definition of obesity (body mass index ≥ 26) in both males and females. For a better answer to the threshold question in a population with obesity and diabetes patterns more like those in the general US population, a very large prospective study would be necessary. The Helsinki Social Security Study of almost 20,000 men and women followed for 12 years for doctor-diagnosed diabetes clearly shows that diabetes risk in both sexes is slightly increased even in persons somewhat less lean compared with the leanest cohort (13). Joslin may not have overstated the case when he wrote in 1921 that persons below the standard weight might bear the legend "immune to diabetes" (2, p. 82).

It is generally accepted that both the degree and the duration of overweight increase the risk of diabetes. The importance of lifetime maximum weight was noted by Olgive (14) in 1935 and the importance of obesity prior to onset by Joslin et al. (15) in 1936. More recently, several investigators, particularly Keen (16) and Knowler et al. (12), have reemphasized that current

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weight is generally a poorer predictor of non-insulin-dependent diabetes mellitus than previous weight, presumably because of the frequency with which weight loss precedes the diagnosis of diabetes. Surprisingly few studies have examined other possible patterns of lifetime body weight as precursors of diabetes.

Fat distribution seems to be a better corollary of diabetes than relative weight or body mass index. Like most other ideas about diabetes, this one is not new. In a 1927 paper on obesity and diabetes, Allison (17) noted the inevitable weight gain and *spherical shape* of those prone to rich food, little exercise, and diabetes. Data were first provided in 1956 by Vague et al. (18), who suggested that the male upper body fat (apple) distribution had greater pathogenic potential than the female lower body fat (pear) distribution. (Epidemiologists are well known for chastizing those who compare apples and oranges. It appears, however, that we have been comparing apples and pears!) Since that time, the apple-android-diabetic and the pear-gynoid-nondiabetic fat distributions have been affirmed, using a variety of relatively simple and epidemiologically applicable measurements of centrality such as subscapular versus triceps skinfolds or waist-hip ratios. For example, in 1969, Feldman et al. (19) reported a case-control study of 360 diabetic and 934 nondiabetic adults matched on race, sex, age, height, and weight whose voluntary multiphasic screening at Kaiser Permanente included a modified glucose tolerance test and multiple skinfold measurements. Compared with those without diabetes, diabetic women showed a significant shift toward a central or masculine fat distribution.

More recently, body fat distribution has been shown to predict incident diabetes independent of body mass index. One elegant study is the 13.5-year follow-up of 792 54-year-old male residents of Göteborg, Sweden (20); body mass index and waist-hip ratio each made a contribution to the probability of diabetes.

Haffner et al. (21) proposed that different measures of fat distribution make independent contributions to diabetes risk. Alternatively, the observed risk ratio differences may reflect simply the benefit of multiple measurements (of obesity or fat distribution) when misclassification occurs with a single measurement.

The location of body fat may also provide indirect clues about the relative importance of obesity early or late in life. It is now well known that early onset obesity is associated with hyperplasia of adipocytes and that late onset obesity is associated with hypertrophy. It is the latter type of fat cell that is associated with insulin resistance (with or without impaired glucose tolerance or diabetes). It is also clear that central adiposity occurs with age and overweight in both sexes and that it is characterized by large fat cells. Less well appreciated, perhaps, is the observation that with moderate (<10 kg) weight loss, fat cell size shrinks but the fat distribution changes very little (22). This may have some relevance to the absence of expected benefits of weight loss, described below.

ARE DIABETES AND OBESITY INHERITED TOGETHER?

Strong evidence that non-insulin-dependent diabetes is hereditary comes from twin studies, in which there is a much higher concordance for monozygotic twins than for dizygotic twins and for non-insulin-dependent diabetes than for insulin-dependent diabetes (23). The role of heredity has also been studied in families. Kobberling and Tillil (24) calculated that siblings of a non-insulin-dependent diabetic proband would have a 38 per cent prevalence of diabetes if they survived to age 80.

The familial pattern is not explained by concordance for overeating or overweight. For example, Barnett et al. (25) found a surprising lack of concordance for obesity in 21 identical twins concordant for non-insulin-dependent diabetes mellitus. In over half of the twin pairs, weight at diag-

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nosis differed appreciably (up to 10 kg) between twins; in some instances, concordance occurred when neither twin was overweight, and in 12 pairs, the twin who weighed less was the first to develop diabetes.

Neel (26) has proposed that the very high prevalence of diabetes in American Indians and similar populations reflects the "telescoping of genetic adjustment" to their recent and sudden transition from the marginal existence of hunter-gatherers to a more affluent and nutritionally assured lifestyle. Certainly, the bimodal distribution of glucose intolerance in very high-risk populations such as the Pimas (27) and the Nauruans (7) suggests a separate genetic condition, in contrast to a simply skewed glucose distribution which could reflect the effects of age and environment per se. Although high-risk populations for diabetes may have marked obesity as a frequent and possibly necessary covariate, studies of the Pimas compared with Caucasians in Rochester, Minnesota (12), and of Mexican Americans compared with San Antonio Anglos (28) show a residual excess risk of diabetes after controlling for the level of obesity.

These data suggest that obesity promotes diabetes in the genetically susceptible, but that obesity is neither a necessary nor sufficient cause of non-insulin-dependent diabetes. If this is true, diabetes should require a larger genetic burden to become apparent in the absence of the additional insult of obesity. Family studies reported by Kobberling (29) and by Baird (23) support this thesis. Kobberling studied diabetes in the siblings of diabetics: Siblings of the more overweight probands with non-insulin-dependent diabetes were least often affected, and siblings of the leanest diabetics were most often affected. Similar results were reported by Baird (23) in a study of 238 new diabetics aged 45–65 years, their nondiabetic siblings, and siblings of nondiabetic controls. (Controls were matched for age, sex, social class, and obesity with the diabetic proband.) The rate of diabetes in the siblings was higher when the diabetic proband was not obese (15.0 per cent) than when the diabetic proband was obese (7.3 per cent). Rates of diabetes were lower in the siblings of nondiabetics, whether they were obese (4.1 per cent) or not (3.4 per cent). The prevalence of diabetes in the obese sibling of a nonobese diabetic was 30 per cent, compared with 10 per cent in the obese sibling of an obese diabetic. These data, which suggest an additive action of genes and obesity (obese persons requiring less genetic susceptibility to develop diabetes than lean persons), are also compatible with observations in the Pimas (12). In this group, the rate of development of diabetes in the most obese is greatest at younger ages, while in less obese subsets, the risk of diabetes increases with age. It is inferred that the most obese who do not develop diabetes early are much less genetically susceptible.

Until recently, evidence that obesity is hereditary was limited. Twin studies showing higher concordance among monozygotic than dizygotic twins suggested high heritability (30), but it was difficult to exclude the role of similar eating and exercise patterns. Studies of adoptees by Bouchard (31) and by Stunkard et al. (32) are more convincing. Bouchard found statistically significant interclass correlations for body mass index, sum of skinfolds, and fat mass in 370 biologic siblings and no association in 120 adopted siblings. Stunkard et al. studied 540 adult Danish adoptees and found a strong correlation between the weight class of the adoptee and the biologic parents, but no relation between the weight class of the adoptee and the adoptive parents, suggesting the possibility that the diabetes gene(s) causes obesity.

Since both obesity and diabetes are common, are they inherited in combination more often than would be expected by chance? The best epidemiologic evidence that diabetes combined with obesity may be inherited comes from the paper by Pettitt et al. (33), who studied the childhood weights of Pimas of normal birth

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weight. Obesity was significantly more common in the children whose mothers had diabetes compared with those whose mothers did not. This observation also fits with the thrifty gene hypothesis which implies that the diabetic genotype should manifest itself early in life, as well as with the observation that the antilipolytic effect of insulin is exaggerated in Pimas (34).

Does diabetes cause obesity?

In 1968, Bierman et al. (35) asked whether long-standing obesity leads to carbohydrate intolerance, whether diabetes causes obesity, or whether obesity and diabetes are related by some common denominator. The possibility that diabetes causes obesity is not new; indeed, 25 years ago, respected proponents used the term "diabetes premellitus" to describe the obese adult with early glucose intolerance (36). The question persists. In 1982, Baird wrote, "On the one hand, it is considered that obesity is an integral part of the diabetic state, the result rather than the cause of diabetes, and, on the other hand, that obesity is diabetogenic in those genetically predisposed to the disease" (23, p. 234). The hypothesis that obesity promotes diabetes is based on the epidemiologic studies reviewed above, the fact that "simple obesity" is characterized by insulin resistance and hyperinsulinemia, and the fact that weight loss sometimes restores glucose metabolism to normal. However, because insulin is the major determinant of fat deposition in adipocytes, the high insulin levels characteristic of insulin resistance could promote obesity leading to diabetes. The demonstration of excess weight in Pima offspring of diabetic mothers, noted above, suggests that it would be premature to exclude the possibility that one or more heritable factors lead to both diabetes and obesity.

Given impaired glucose tolerance, does obesity increase the risk of diabetes?

It is well known that overweight adults often have impaired glucose tolerance and that glucose intolerance increases the risk of diabetes. Studies of the effect of obesity on risk of worsening to diabetes, given impaired glucose tolerance, however, have given divergent results. For example, in the Bedford 10-year follow-up study of 241 adults with impaired glucose tolerance, obesity increased the risk of worsening to diabetes, but not before the second five years of follow-up (37). (Over half of overweight subjects later had substantially improved glucose tolerance.) In the Whitehall 10-year follow-up study of 204 men with impaired glucose tolerance, blood glucose but not obesity was independently predictive of worsening to diabetes; higher glucose levels were apparently necessary to promote diabetes in those who were either the leanest or the most overweight at baseline (38). In a five- to 12-year follow-up of 288 Japanese subjects with impaired glucose tolerance, Kadowaki et al. (39) found that subsequent diabetes was associated with maximum body weight (although not in a linear fashion), and this association was independent of other risk factors including fasting and two-hour blood glucose and insulin response. In O'Sullivan and Mahan's (40) 10- to 16-year follow-up study of women with normal postpartum glucose tolerance, the cumulative incidence of diabetes was significantly higher in women with transient gestational diabetes than in those without; in the former, it also was significantly higher in those who were overweight. Thus, these data, although inconsistent, generally suggest an increased risk of diabetes in overweight versus lean adults with impaired glucose tolerance.

Although weight loss improves glucose tolerance in the short term, evidence that it prevents worsening to diabetes is surprisingly sparse. Berger et al. (41) studied 70 grossly obese patients with impaired glucose tolerance who were placed on weight reduction diets and followed for five years. Half showed a normalized glucose tolerance, and half showed further deterioration, including 10 in whom diabetes developed. The progression and normalization

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groups were similar with regard to initial age, height, weight, and degree of glucose intolerance, but the normalization group had an average weight reduction of 22 per cent, and the progression group lost an average of only 9 per cent of their original weight. Of interest to the interventionist, the benefit attributed to weight loss was limited to patients less than 50 years of age.

Toeller et al. (42) followed 29 very obese adults with impaired glucose tolerance for 10 years, obtaining measurements of weight and a repeat glucose tolerance test at five and 10 years. Those who lost weight initially were more likely to have normal glucose tolerance, and those who gained weight were more likely to develop diabetes. Nevertheless, and despite successful weight loss, at 10 years 38 per cent had diabetes, and only 17 per cent had returned to normal glucose tolerance.

Given diabetes, does obesity increase the risk of complications?

The only study that has systematically correlated body weight with both micro- and macroangiopathy in diabetics is that of Pirart (43). He studied 4,398 known diabetics in Brussels and followed a diminishing fraction of this group for up to 25 years. There was a statistically significant excess prevalence of retinopathy and nephropathy in overweight persons who had diabetes of up to 15 years duration (compared with diabetics of more normal weight); numbers were too small for meaningful comparisons when diabetes had been known for more than 15 years. Present obesity was related to past obesity, but results were more consistent when analyzed by maximum prediabetic, rather than by current, weight. The prevalence of coronary and peripheral arterial disease, however, was unrelated to current or maximum weight.

Using the Rochester, Minnesota, data base, Ballard et al. (44) reported that marked obesity was an independent risk factor for retinopathy in 1,031 adults with non-insulin-dependent diabetes mellitus, but the association was not stepwise or statistically significant in univariate analysis. The opposite was reported by Knowler et al. (45) in the Pimas, in whom the incidence of hemorrhagic retinopathy was inversely related to tertiles of body mass index. In a Wisconsin population-based study of 1,370 patients with diabetes diagnosed at age 30 or older, diabetic retinopathy was not significantly related to current body mass index (46).

Only two publications have addressed the question of overweight as a predictor of mortality in diabetics. In the Rochester, Minnesota, study, survivorship was slightly better in overweight diabetics, but ascertainment bias could have led to selective diagnosis of less severe diabetes in overweight patients (47). The University Group Diabetes Program (48) data permit an analysis of the 10- to 14-year follow-up all-cause, cardiovascular disease and cancer mortality by categorical baseline weight in the placebo and insulin-treated groups, all of whom had glucose intolerance or non-insulin-dependent diabetes mellitus by current criteria. The more overweight group did better than the more normal weight group in almost every instance.

Studies showing a better prognosis in lean diabetics fit the conventional wisdom, but studies showing a better prognosis in overweight diabetics are compatible with a larger genetic burden in the lean adult with non-insulin-dependent diabetes (see above), which presumably increases the risk of diabetic complications. The inconsistent results noted above do not suggest any single explanation, but they do raise some serious questions about the conventional wisdom.

Given diabetes, does weight loss improve the survival?

Until recently, it was a matter of faith that earlier detection and treatment would prevent or delay complications and improve survival in patients with non-insulin-dependent diabetes mellitus, the majority of whom are overweight.

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There is no question that weight loss is associated with improved blood glucose and other heart disease risk factors such as blood pressure and plasma cholesterol (49). Since glucose homeostasis is "good," and heart disease is the major cause of mortality in adult diabetics, it seems logical to expect that weight loss would reduce all-cause and cardiovascular disease mortality in diabetics. This expectation, which drives most of the medical management of overweight patients with non-insulin-dependent diabetes mellitus, has not been tested specifically in a clinical trial or in a published observational study.

The University Group Diabetes Program (48) study, while not a trial of weight loss per se, does provide extensive clinical trial data related to weight loss and mortality. (The value of this study has been obscured by the controversial findings in the tolbutamide-treated group, which will not be considered further here.) Three other intervention groups (placebo, insulin standard, and insulin variable) received dietary advice, but sustained weight loss was seen only in the placebo group, improved metabolic control was achieved only in the insulin variable group, and the insulin standard group had neither improved control nor weight loss. The all-cause and cardiovascular heart disease mortality in these three groups was virtually identical during a 10- to 14-year follow-up.

Indeed, the life and death consequences of weight loss, always assumed to be positive, have only recently been studied even in nondiabetics. Sidney et al. (50), in the Kaiser Permanente group, found that thinness was associated with increased all-cause mortality only in smokers, but that there was an association of long-term weight loss with increased mortality in thin and average weight men and in thin women.

The association between weight change and all-cause mortality was also examined in 875 persons aged 50–94 years from Alameda County, California (51). After exclusion of those who had major chronic conditions and after adjustment for baseline body mass index, the association between weight change (1965–1974) and all-cause or cardiovascular disease mortality (1974–1983) showed the maximum risk to be in those who lost weight. A 14-pound loss carried a relative hazard of all-cause mortality of 1.48 (95 per cent confidence interval 1.18–1.85). The strength of the association was not changed by adjusting for age, sex, cigarette smoking, alcohol use, depression, social isolation, or income. Although smokers lost more weight on average than nonsmokers, there was no significant interaction between cigarette smoking and weight change with respect to mortality. There was no similar increased risk associated with weight gain. These data, at the minimum, suggest that intervention programs promoting weight loss among older persons may not confer benefit. Because those with chronic disease were excluded, these data may not pertain to weight change in those with diabetes, however.

Data from another study, by Bloom et al. (52), do consider diabetes. These authors examined the impact of weight change over six years in 6,111 Japanese-Hawaiian men aged 51–74 years who were free of cardiovascular disease and cancer at baseline and six-year examination and who were followed for another six years (12 years in total). Incidence rates for all-cause mortality and for cardiovascular disease (fatal and nonfatal separately or combined), adjusted for baseline body mass index, were highest among the men who lost the most weight. Among those who gained the most weight, there was a slight statistically insignificant upward trend. The risk of all-cause mortality was 60 per cent greater and the risk of heart disease mortality was 40 per cent greater for men in the highest quintile compared with the fourth highest quintile of weight change. Removing early cases of cardiovascular disease did not alter these associations. Neither the effect of being on a diet (weight loss or any type) nor change in cigarette smoking status altered the as-

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sociation. Diabetes was examined specifically. There were 1,441 men with diabetes at the baseline examination and 413 subsequent incident cases, for a total of 1,854 men with diabetes. Diabetics as a group lost an average of 1.9 pounds compared with nondiabetics, who lost 0.7 pounds. On average, new diabetics lost 2.4 pounds; those on antidiabetic medication lost 3 pounds, and those on a diet alone lost 5 pounds. When the association between weight change and coronary heart disease incidence or death was examined by diabetic status, there were highly significant associations between amount of weight lost and total coronary heart disease, fatal coronary heart disease, and total mortality in diabetics. (Among nondiabetics, there was no significant association between weight change and coronary heart disease, but there was an association between weight loss and total mortality.) When examined by quintiles of weight change, diabetics in the first quintile who lost the most weight (12.3 pounds) had the highest rates of total coronary heart disease (68/1,000), coronary heart disease death (31/1,000), and total mortality (81/1,000), while men in the fourth quintile, who gained an average of 2.4 pounds, had the lowest rates of total and fatal coronary heart disease—37/1,000 and 9/1,000, respectively. In a regression model, the glucose level-weight change interaction was significant for all endpoints. In the same cohort, weight loss was accompanied by the expected improvement in atherogenic traits.

These observations cannot exclude the possibility that those who lost weight were already ill, but they are equally compatible with the possibility that weight loss in diabetics has a negative effect. They must certainly raise some questions about the universal recommendations for weight loss in overweight patients with non-insulin-dependent diabetes mellitus. They also suggest another critically important area for future research that can be done best by epidemiologists.

Conclusions

Obesity is the best recognized risk factor for non-insulin-dependent diabetes mellitus, but many details of the association remain to be worked out. Although the duration of obesity and previous overweight are more important than current overweight, the relation of childhood and adolescent overweight to the risk of diabetes in later life needs analysis. Similarly, although overweight is associated with poor glucose tolerance and hyperinsulinemia, which are often reversible in the short term with weight loss, the long-term benefit of weight loss on both the risk of diabetes and the risk of death or complications has been, given diabetes, studied only rarely. Lack of such studies possibly reflects the infrequency with which diabetics are able to sustain weight loss. Resistance to weight loss raises the issue of whether the genes for obesity and diabetes are the same in older adults, as well as the possibility that rigorous control of diabetes promotes weight gain. There are clearly a large number of etiologic hypotheses waiting to be tested; epidemiologic studies of populations will be necessary since other samples are weighted by the propensity to selectively test for diabetes only in overweight subjects. The relatively recent availability of standardized diagnostic criteria for non-insulin-dependent diabetes should greatly facilitate such studies (whether or not there is universal agreement on the best criteria for clinical classification and intervention). Tests of the therapeutic implications of long-term weight control or weight loss may need to await improved methods of achieving and maintaining leaner weights in older diabetics.

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