

# Weight Loss and Mortality in Type 2 Diabetes

A guiding principle in the treatment of obese type 2 diabetic patients has been the recommendation to lose weight (1). The rationale for such advice has been clear. Type 2 diabetes is both an insulin-resistant state and a disease in which the  $\beta$ -cells of the pancreas gradually lose their ability to secrete insulin. Insulin resistance leads to a greater need for the hormone, and the pancreas cannot keep up with the demand. Of type 2 diabetic individuals in this country, 85–90% are obese, and obesity is also an insulin-resistant state. As a result, obesity abets the development of diabetes and, once diabetes manifests itself, accelerates its deterioration. With weight loss, most (though not all) people with diabetes improve their insulin sensitivity. This improvement lowers the demand for insulin, thereby giving the  $\beta$ -cells a reprieve from such a demand. There is very good evidence that, in the short term, glucose and HbA<sub>1c</sub> levels improve (2,3). In the longer term, there are conflicting results: some studies show a sustained effect (4); others do not (5). However, the recent report from the Swedish Obesity Study (SOS) (6) has shown dramatic results with surgical weight loss in both the development and the progression of diabetes in very obese patients (BMI  $\geq$  34 and 38 kg/m<sup>2</sup> in men and women, respectively). A question concerning the improvement of glucose control is whether the amelioration is really due to the reduced weight or to a decrease in total calorie and carbohydrate flux through the body with the restriction of food intake (3,7). Certainly, many of the beneficial effects on glucose control begin to occur when body composition has not changed very much and the fat burden is still very high (2,3). Nevertheless, regardless of the mechanism, the evidence for an improvement in diabetes control with weight loss is very strong.

There are few data, however, regarding the effect of weight loss on mortality in type 2 diabetes. One study (8) has reported a prolongation of life in a group of Scottish diabetic patients who lost weight. However, this was a retrospective rather than a prospective study, and the number of patients was small. The study by Williamson

et al. (9) in this issue of *Diabetes Care* is a more systematic effort to address the issue of the effect of weight loss on mortality in type 2 diabetic patients. Williamson et al. focused on intentional weight loss. To differentiate intentional from unintentional weight loss is very important because there are many reasons to believe that unintentional weight loss in diabetic patients is related to poor glucose control, complications of the disease, or simply other diseases that begin to occur in this generally more elderly population group. Such unintentional weight loss related to progression of disease would be expected to increase mortality. The natural history of weight in type 2 diabetic patients is not clear. For instance, data from the Pima Indians show a progressive increase in weight with age until they develop diabetes, at which time their weight begins to decrease (10). On the other hand, the U.K. Prospective Diabetes Study showed that after an initial weight loss with dietary instruction, type 2 diabetic patients showed a gradual increase in weight gain over a period of 15 years (11). Whether a diabetic patient gains, maintains, or loses weight after diagnosis seems to depend on a combination of factors, including diet, physical activity, the degree of glucose control, the progression of complications, and the development of other diseases. Therefore, defining what is intentional and what is unintentional weight loss in a diabetic population, despite the possible difficulty of doing so, is extremely important in assessing its health impact.

The American Cancer Society Study began in 1960. The diabetic individuals in this cohort are the subjects referred to in the present article by Williamson et al. (9). Information on weight change was by self-report. The median follow-up was 12.9 years for survivors and 7.1 years for descendants. Intentional weight loss was associated with a 25% reduction in total mortality (relative ratio [RR] +0.75, 95% CI 0.67–0.84) and a 28% reduction in cardiovascular disease plus diabetes mortality (RR +0.72, 95% CI 0.63–0.82). The largest reductions in mortality occurred with intentional weight loss of 20–29 lbs (a decrease of 33%); weight loss of >70 lbs was associ-

ated with small increases in mortality. Thus, this analysis suggests a strong effect of moderate intentional weight loss on mortality in type 2 diabetic patients. This gives credence to the notion that overweight diabetic patients should attempt to lose weight.

Because the cohort was followed for an average of 12.9 years, there is a strong possibility that the weight loss effect was successful in curbing mortality, even though it is likely that many of the patients regained some or all of the weight they lost. This possibility suggests a “memory” effect of intentional weight loss, which may be sustained for a long duration even if the weight loss is not fully maintained. A key question, which cannot be answered from the study, is whether a much greater effect on mortality reduction would have been found if the weight loss had been sustained during the 13 years of the study.

An interesting question raised by this study is whether the beneficial effect of weight loss in overweight type 2 diabetic patients has a limit. Individuals who lost >70 lbs actually experienced small increases in mortality. Thus, it is possible that too radical a weight drop may initiate untoward metabolic responses. The SOS study may help to resolve this question, because weight loss in these patients, although it is on average 28 kg at 2 years of follow-up, has been much greater in some patients than in others (6). Comparative mortality rates may be calculated, although the study may not have actual statistical power for such a differentiation of weight loss effects.

A commonly asked question is at what point should doctors intervene in overweight diabetic patients. Is there an equal benefit of weight loss in a diabetic patient with a BMI of 27 kg/m<sup>2</sup> and a patient with a BMI of 41 kg/m<sup>2</sup>? Opinions on this question vary. One of the arguments relates to the presence of insulin resistance in overweight individuals. Studies such as those on the Pima Indians (12) suggest that there is an effect of increasing weight on insulin resistance to a BMI of  $\sim$ 35 kg/m<sup>2</sup>, after which insulin resistance tends to plateau. Other studies, however, have documented continued increases in insulin resistance as

obesity increases (13). If the former is true, one might expect a stronger effect of weight loss on diabetes control and mortality in patients with BMIs between 25 and 35 kg/m<sup>2</sup>; if the latter is true, all weight categories would be improved. In fact, Williamson et al. found that, compared with subjects with an initial BMI of 27–29 kg/m<sup>2</sup>, the age-, sex-, and smoking-adjusted mortality rates were 5–25% higher with increasing levels of initial BMI.

The importance of the quality of the weight loss in a diabetic patient is also not addressed in this article. We have recently analyzed two nondiabetic data sets (Tecumseh and Framingham) and have found that decreases in mortality correlate with a loss of fat and increases in mortality correlate with a loss of lean body mass (14). We also know that overweight people who are overmuscular and not overfat do not have the insulin resistance and cardiovascular risk factors of those who are overfat (15). This question of the effect of differential body compartment change on morbidity and mortality begs for more investigation.

Investigations on whether there is an age limit beyond which weight loss yields diminishing returns on outcome generally focus on age 65 years and older. The present cohort was aged 40–65 years and, therefore, will not provide any conclusions to this important issue. We will require further longitudinal (or retrospective convenience sample) studies to obtain guidance on this topic.

In this cohort, physical activity was inversely related to mortality. The literature on the positive impact of physical activity in reducing the development of type 2 diabetes is strong (16), but the long-term effect of physical activity on morbidity and mortality in type 2 diabetic patients has not been well tested in a long-term prospective randomized clinical trial.

In summary, this important report strengthens the rationale for the guidelines of numerous diabetes associations around the world that state that weight loss should be a primary recommendation for overweight type 2 diabetic subjects and that physical activity is also helpful in the management of type 2 diabetes. Significant data support the notion that improved glucose

levels reduce progression of microvascular disease, and there are data to suggest that weight loss improves glucose control. Whether intentional weight loss and physical activity directly affect diabetes morbidity has not been adequately tested; such an examination will be conducted in the National Institutes of Health-supported Study of Health Outcomes of Weight Loss, which has recently begun. It is reassuring, nevertheless, to have the first solid evidence, as provided in the article by Williamson et al. (9), that moderate intentional weight loss in type 2 diabetic patients reduces mortality.

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