Weight and non-insulin-dependent diabetes mellitus\(^1,2\)

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**ABSTRACT** I review the effect of weight on the prevalence of non-insulin-dependent diabetes mellitus (NIDDM) and of its associated conditions. Weight loss decreases morbidity in diabetic patients. The effect of weight loss on mortality also is favorable, although the number of reports in which this has been studied is small. The recommendation is made that persons with NIDDM who have a body mass index (BMI, in kg/m\(^2\)) > 25 should try to lose weight to at least that level. Those with BMIs between 20 and 25 should make every effort to maintain their present weight throughout life. *Am J Clin Nutr* 1996;63(suppl):426S–9S.

**KEY WORDS** Diabetes, obesity, weight, body mass index

**INTRODUCTION**

The relation between the average weight of a population and the prevalence of diabetes mellitus was shown many years ago in several cross-sectional studies (1, 2). In the data from the second National Health and Nutrition Examination Survey, the relative risk of developing diabetes was 2.9 times greater for obese persons 20–75 y of age than for normal-weight persons (3). The relative risk was 3.8 for those 45–75 y of age and 2.1 for those aged 20–45 y (3). In Pima Indians, there is a strong correlation between increasing weight and both the prevalence and incidence of diabetes (4). In a prospective Scandinavian study, moderate obesity was associated with a 10-fold greater risk of developing diabetes (5). In two more recent studies, one in men and the other in women, a clear relation was found between increasing weight and increasing incidence of diabetes (6, 7).

**RISK FACTORS**

Vague (8) was the first to describe the importance of distribution of body fat to health risk in the 1950s, noting the association between central obesity and diabetes mellitus. In more recent years, there has been increasing evidence that his observations, which were initially ignored, are correct. The effect of central (or visceral) abdominal obesity on diabetes has now been described in several cross-sectional studies (9–11). Ohlson et al (12), in an 8-y longitudinal prospective study, found that central obesity imposed an increased risk of developing diabetes, which was greater than the risk of adiposity per se. Lundgren et al (13) and Haffner et al (14) reported similar increased risk.

Studies in the Pima Indian population have shown that the increase of diabetes incidence with a positive family history is additive to the effect of body weight (4). There is also a positive effect of age (15), which also is additive to the effect of weight. Some of this age effect may be related to the increased adiposity that occurs with maturity, as well as to the increased central obesity that generally develops in many older persons (16).

**WEIGHT LOSS AND INSULIN REGULATION**

The effect of weight on mortality in diabetic patients has been studied only sparingly. This is because over the years in most prospective studies in which the endpoint was mortality, patients with diabetes were excluded. Weight reduction has been advocated for overweight diabetic patients as reasonable knowledge of the pathophysiology of the disease has accrued. Obesity enhances insulin resistance (17, 18). It has been shown repeatedly that weight reduction improves blood glucose control in diabetic subjects (19–24). There is clearly an effect of restriction of energy intake that is independent of weight reduction because improved glucose control occurs very quickly, before much weight reduction and change in body composition occurs (24); however, the effect of weight loss is strong. As weight loss occurs, concentrations of glycosylated hemoglobin drop (25, 26). Patients have been able to stop taking insulin and can even be managed without hypoglycemic agents (21). Even a 5% loss of weight decreases prevailing blood glucose concentrations (25). In the U.K. Prospective Diabetes Study, the patients who lost more weight showed the best glucose improvement, but to lower glucose to normal, a weight loss of an average of 18 kg was required (27).

Weight loss improves insulin sensitivity. Both peripheral insulin sensitivity and the ability of insulin to suppress hepatic glucose output are improved as weight is lost (28). All aspects of glucose uptake into muscle and adipose tissue are improved with weight loss. There is improved binding of insulin to its receptor (20, 29). Also, glucose transport into isolated muscle strips is greatly improved (30). Tyrosine kinase activity in adipocytes is also improved after weight loss (31), thereby activating insulin effects within the cell. In addition, hepatic glucose output is diminished.

The effect of weight loss on insulin secretion in diabetic patients depends on the amount of insulin secretory response

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left in the β cells of the pancreas. β cells initially secrete increased insulin and C-peptide with the onset of obesity because the pancreas compensates for the increased insulin resistance by releasing more insulin (32). Insulin remains elevated until the β cell begins to fail, at which time insulin secretion begins to drop and diabetes supervenes (33). Generally, weight loss, as it improves insulin sensitivity, decreases the demand on the insulin secretory system. Also, because sustained hyperglycemia impairs the β cell insulin response to a given glucose concentration (so-called glucose toxicity) (34, 35), the lowering of blood glucose concentrations with weight loss increases the insulin secretory response. The net effect is generally to decrease insulin secretion, thereby reducing the stress on the pancreas and improving metabolic control.

DIRECT AND INDIRECT EFFECTS OF WEIGHT REDUCTION

The relation of weight loss to morbidity has been reported by many. Long et al (36) showed that obese patients who underwent bariatric surgery and sustained their weight loss had significantly lower rates of progression to diabetes than did untreated control subjects. The rates were 0.15 cases/100 person-years for the surgery patients compared with 4.7 cases/100 person-years for the matched control subjects who did not undergo weight loss. Also, in the Nurses Health Study, a subgroup of women whose body mass index (BMI) was > 27 at baseline and who lost 5–20 kg in the subsequent 4 y had a 30% reduction in the risk of developing NIDDM compared with women whose weight did not change > 1 kg (37). In another study carried out in Malmo, Sweden, a group of persons with impaired glucose tolerance was placed on a program of weight loss and increased physical activity (38). The treatment group lost 6 kg at the end of 1 y and maintained a weight loss of 2.0–3.3 kg at 5 y, whereas the control group gained 0.2–2.0 kg. At 5 y, 21% of the control group had developed diabetes whereas only 11% of the weight-loss group had become diabetic.

In addition to the direct effect of weight loss in decreasing hyperglycemia, there is also an effect on the comorbid conditions that often accompany diabetes. About one-third of patients with NIDDM have hypertension, which improves with weight loss. Although the exact pathophysiology of this phenomenon is not fully understood, some of the lowering of blood pressure occurs through a decrease in insulin resistance, a decrease in insulin concentrations, and a resulting decrease in sodium reabsorption in the kidney by insulin (39). Because hypertension abets the vascular complications of diabetes, it has been a cardinal aim of diabetes therapy to keep blood pressure normal (40). An impressive number of studies have reported an improvement in blood pressure in obese and diabetic patients who have lost weight (23, 41–44). This is true of both systolic and diastolic pressure (23, 44).

A large percentage of patients with NIDDM have dyslipidemia (45). This disorder is characterized by elevated very-low-density lipoproteins (VLDLs), leading to hypertriglyceridemia (46). There is overproduction of VLDL triglyceride and VLDL apolipoprotein B, and also a defect in VLDL clearance (47). The composition of low-density lipoprotein (LDL) particles is altered: smaller and denser particles are present, which are significantly more atherogenic (48). In addition, the elevated prevailing glucose can enhance the glycosylation of the LDL particles, making them significantly more atherogenic (49). An increased susceptibility of the LDL particles to oxidation has also been reported; this susceptibility also makes them more atherogenic (50).

Finally, high-density-lipoprotein (HDL) production seems to be decreased in diabetes, so that circulating concentrations are lower (47). Weight loss has been found to improve all of these lipid abnormalities (21–23, 44, 45, 50, 51), making weight reduction a primary intervention for ameliorating the dyslipidemia of diabetic patients (45, 52).

UNINTENTIONAL WEIGHT LOSS AND MORTALITY

The relation of weight loss to mortality is complicated in NIDDM by the fact that many diabetic patients lose weight unintentionally as their disease becomes more severe and as they develop complications such as kidney failure and heart disease. Thus, the weight loss is directly related to the increasing severity of their disease. It would therefore be natural that weight loss in this group of patients be associated with increasing mortality. This is clearly involuntary weight loss due to illness and not voluntary weight loss initiated by the patient early in the disease in an effort to improve morbidity.

Few studies of weight loss early in the disease that have specifically focused on subsequent mortality are available. In the Malmo study, the investigators intervened with diet and exercise in a group of diabetic subjects and followed them for 5 y (38). Although sustaining only a modest weight loss, the mortality of the patients dropped lower than the mean for the general population (3.2% compared with 3.7%). Although a difference between 3.2 and 3.7 is not biologically meaningful, the fact that mortality in the NIDDM patients matched that of the general population certainly is. The diabetic patients who did not lose weight had, on the other hand, a mortality of 11.9%. There are few other studies on diabetes and weight loss in which mortality was an endpoint because as mentioned previously diabetic patients have been systematically excluded from such long-term prospective studies. A retrospective study was undertaken by Lean et al (53) on 263 NIDDM patients who died over a 2-y period. Their life expectancy was found to be 35% lower than independently published figures for the general population. The calculation was made that for each 1 kg of weight loss in the first year of diagnosis, there was an associated 3–4-mo increase in survival. Lean concluded that a 10-kg weight loss could revert life expectancy to that of the normal population (53).

SUMMARY

Overall, it is evident that weight loss improves morbidity in diabetic persons. The effect of voluntary weight loss on mortality has been studied much less frequently but a beneficial effect is also suggested, although more studies are needed. As a result, because the incidence of diabetes continues to drop as BMI decreases, even below 20 (6), it seems reasonable to recommend that persons with NIDDM who have BMIs > 25 try to reduce their weight to at least that figure. If their BMI is between 20 and 25, they should make every effort to maintain
their body weight at its present level and not to gain any weight throughout the rest of their life.

REFERENCES