Mortality and Morbidity Associated With Body Weight in People With IDDM

The WHO Multinational Study of Vascular Disease in Diabetes

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OBJECTIVE — Strict glycemic control in people with insulin-dependent diabetes mellitus (IDDM) reduces the risk of microvascular complications, but improvements in control are also associated with weight gain. Fears about the mortality risks of obesity may limit the acceptability of tight control. Therefore, we examined morbidity and mortality risks associated with body weight in people with IDDM.

RESEARCH DESIGN AND METHODS — This was a cohort study of 644 men and 576 women with IDDM from nine centers worldwide. Baseline examinations were performed in 1975–1977, and mortality follow-up continued until 1988.

RESULTS — Body weight was positively associated with blood pressure and, in men, with cholesterol. Fasting blood glucose was higher in the most obese groups in women only. There were 204 deaths among the men and 148 among the women. There was a reverse J-shaped relationship between body weight and all-cause mortality, with the highest mortality rates occurring in the leanest body mass index (BMI) category. The age-, duration-, and center-adjusted mortality rate ratio (95% confidence interval) comparing BMI category <20 kg/m^2 with BMI category ≥ 22 and <24 kg/m^2 was 2.64 (1.59–4.38) in men and 1.54 (0.77–3.06) in women. Additional adjustment for smoking, blood pressure, glucose, cholesterol, and proteinuria did not qualitatively alter these findings.

CONCLUSIONS — We conclude that except in very lean people with IDDM, body weight is not significantly associated with mortality. Thus, efforts to improve glycemic control should not be restricted by concerns about the effects of weight gain on mortality.

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BMI, body mass index; CI, confidence interval; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes; WHO MSVDD, World Health Organization Multinational Study of Vascular Disease in Diabetes.

There is now conclusive evidence that strict glycemic control in people with insulin-dependent diabetes mellitus (IDDM) reduces the risk of microvascular complications (1,2). However, incorporation of these findings into practice may be constrained by reservations about costs to the health service and the increased frequency of severe hypoglycemic episodes associated with this degree of control (3). A more frequent metabolic problem is weight gain, which has a direct relationship with the strictness of glycemic control (4,5). This weight increase may counteract the benefits of improved glycemic control (4,6) because, in the general population, it is associated with lipid disturbances and higher blood pressures (7). Obesity, partially through these mechanisms, may result in an increased risk of death. It is therefore important to evaluate the risks of weight gain and subsequent obesity before implementing costly regimens to improve glycemic control. However, information on mortality risks associated with body weight in people with IDDM is conflicting. Cohort studies that include people with IDDM have variously reported that obesity may be protective (8), that obesity may, at least in women, increase the risk of death (9), or that there is no association between obesity and survival (10). In people with non-insulin-dependent diabetes mellitus (NIDDM), there is a suggestion that weight loss may improve survival (11), but no such data are available for people with IDDM, in whom relationships between body weight and mortality may differ. We examined the relationship between weight and all-cause mortality in a cohort study of people with IDDM.

RESEARCH DESIGN AND METHODS

— Data from the mortality follow-up of the World Health Organization Multinational Study of Vascular Disease in Diabetes (WHO MSVDD) were used (12). This is a cohort study of people with IDDM and NIDDM. Briefly, each center randomly selected ~500 people

with diabetes who were stratified by age-group (age range 35–54 years), sex, and duration of diabetes. Subjects attended their local center for a physical examination between 1975 and 1977. A questionnaire that included information on demographic variables, smoking habits, and past medical history was completed. Sitting blood pressure was measured using a standard sphygmomanometer. Height and weight were measured without outdoor clothing or shoes. An ECG was recorded and coded using the Minnesota code. All centers sampled venous blood for cholesterol. These samples were analyzed by a central laboratory (U.S. Public Health Service Centers for Disease Control and Prevention, Atlanta, GA) for six centers. The remaining three centers (Berlin, Warsaw, and Havana) analyzed cholesterol locally. Eight centers measured fasting plasma glucose locally by different but comparable methods; detailed methods are described elsewhere (13). Urine samples were tested for proteinuria by the salicylsulfonic acid test. Three categories of proteinuria were described: heavy, slight, or none, depending on the degree of precipitation.

Mortality follow-up for this cohort was completed on 1 January 1988. Mean duration of follow-up was 9 years (range 0–14 years). Centers that achieved at least a 95% follow-up rate were London, U.K.; Bern, Switzerland; Warsaw, Poland; Berlin, Germany; Zagreb, Croatia; Hong Kong (until 1 January 1983); Tokyo, Japan; Havana, Cuba; and Oklahoma City, OK. The underlying cause of death was determined by a panel using information from death certificates and, when available, clinical records and autopsy reports (14).

A person with IDDM was defined as someone who was receiving insulin within 1 year of diagnosis. BMI was calculated as the weight (in kilograms) divided by the square of the height (in meters) and then divided into five categories. In the relative risk analyses for mortality, subjects with a BMI between 22 and <24 kg/m^2 (classified here as normal weight) formed the reference category. Current smokers were defined as those who stated that they smoked at the time of the baseline investigation. Narrower smoking categories were used for the mortality analyses: never smoked, ex-smoker, smoker (1–14 cigarettes/day), smoker (15–24 cigarettes/day), and smoker (25+ cigarettes/day).

Statistical analysis

Age-adjusted means of all baseline continuous variables were calculated by least-squares regression models, holding age at its mean value. Age-standardized median blood pressure was calculated by assigning treated hypertensive patients to the upper tail of the blood pressure distribution (15). Age-standardized prevalence rates of smoking and proteinuria used the examined IDDM population as the standard. To determine whether there was a trend across categories of BMI for baseline variables, a chi-squared test for trend was used for categorical data and an F test was used in analysis of variance for continuous data.

Mortality rates, relative risks, and 95% confidence intervals (CIs) were calculated using Poisson regression models in EGRET (Epidemiological Resources, Seattle, WA) (16). Only subjects with complete data on possible confounders were included in these analyses. All deaths (14 men and 4 women) in the first year of follow-up were excluded from the main mortality analyses. Further mortality analyses were performed excluding deaths in the first 3 years of follow-up; this led to the exclusion of an additional 36 deaths of men and 9 deaths of women. A previous myocardial infarction may result in weight loss before death, and approximately half of the deaths in both sexes were due to cardiovascular disease. We therefore excluded all individuals with evidence of major Q waves on ECG at baseline (Minnesota codes 1–1 or 1–2) from the mortality analyses (8 men and 6 women).

RESULTS — BMI ranged from 14.2 to 49.6 kg/m^2 in men and from 14.9 to 46.3 kg/m^2 in women. In men, systolic blood pressure and serum cholesterol were higher in the more obese categories (Table 1). There was no relationship between body weight and fasting plasma glucose. In contrast, for women, significant relationships were observed for both fasting plasma glucose and blood pressure, but not for cholesterol. A greater proportion of men in the leanest BMI group were current smokers (76%) compared with in the most obese group (36%). In both sexes, proteinuria was more commonly found in the most obese and leanest categories of BMI.

There was an inverse J-shaped relationship between BMI and mortality for both sexes, with the highest mortality occurring in the leanest group (Fig. 1). This relationship persisted when adjustments were made for center, proteinuria, and smoking (Table 2). Further adjustment for blood pressure and cholesterol did not substantially alter the risk estimates. There were no significant interactions between confounding variables. Adjusting for fasting blood glucose in the subsample of patients who had this measured did not alter rate ratios in men and did not qualitatively alter them in women (data not shown).

Mortality was lowest in the BMI category of 22 to <24 kg/m^2 in men and 20 to <22 kg/m^2 in women. There was no significant trend in mortality from the lowest mortality group to the most obese group in either men (χ^2 trend 3.3, P = 0.07) or women (χ^2 trend 0.02, P = 0.9).

Mortality rate ratios in the four more obese categories were compared with the leanest after deaths in different follow-up periods were excluded. Adjustment was made for age, duration of diabetes, center, smoking, proteinuria, blood pressure, and cholesterol. In men, excluding deaths in the first year of follow-up, this rate ratio was 0.39 (95% CI 0.25–0.63), and in women it was 0.40 (95% CI 0.20–0.78). Excluding deaths in the first 3 years of follow-up changed these rate ratios to 0.49 (0.30–0.80) in men and 0.53 (0.27–1.03) in women.

Table 1—*Clinical characteristics by category of BMI in men and women with IDDM*

	Category of BMI (kg/m²)					*P* value for trend
	<20	20 to <22	22 to <24	24 to <26	26+	
Men						
n	72	123	185	143	121	—
Age (years)	44 ± 0.7	44 ± 0.5	43 ± 0.4	45 ± 0.5	46 ± 0.5	0.02
Duration (years)	13 ± 1.0	16 ± 0.8	16 ± 0.6	17 ± 0.7	14 ± 0.8	0.002
Cholesterol (mg/dl)	210 ± 6	217 ± 5	224 ± 4	229 ± 5	237 ± 5	0.005
Systolic blood pressure (mmHg)	124 (120–130)	130 (126–136)	130 (128–136)	138 (134–140)	142 (136–150)	0.0001
Plasma glucose (mmol/l)	12.7 ± 1.0	10.7 ± 0.8	13.4 ± 0.6	12.0 ± 0.7	12.0 ± 0.6	0.08
Current smokers (%)	76 ± 5	63 ± 4	52 ± 4	47 ± 4	36 ± 4	0.0001
Proteinuria (heavy, %)	20 ± 5	12 ± 3	12 ± 2	16 ± 3	22 ± 4	0.1
Women						
n	56	101	145	84	190	—
Age (years)	43 ± 0.8	44 ± 0.6	44 ± 0.5	45 ± 0.7	45 ± 0.5	0.1
Duration (years)	15 ± 1.2	17 ± 0.9	18 ± 0.7	17 ± 1.0	14 ± 0.6	0.008
Cholesterol (mg/dl)	229 ± 8	222 ± 6	235 ± 5	233 ± 6	236 ± 4	0.4
Systolic blood pressure (mmHg)	124 (118–134)	130 (120–136)	140 (132–142)	130 (126–140)	142 (138–146)	0.0001
Plasma glucose (mmol/l)	11.4 ± 1.0	11.1 ± 0.8	13.8 ± 0.7	13.5 ± 1.0	14.5 ± 0.6	0.004
Current smokers (%)	24 ± 6	33 ± 5	29 ± 4	25 ± 5	27 ± 3	0.7
Proteinuria (heavy, %)	15 ± 5	9 ± 3	11 ± 3	10 ± 5	14 ± 3	0.7

Data are means ± SE of baseline variables and medians (95% CI) for systolic blood pressure. Data for cholesterol and plasma glucose are age-adjusted. Data for systolic blood pressure, current smokers, and proteinuria are age-standardized.

CONCLUSIONS— This is the first time that mortality by level of body weight has been examined in a large sample of people with IDDM. Earlier studies have been limited by their small sample size (9), their failure to separate the two forms of diabetes (8), or their failure to take into account important confounders, such as smoking. We show that body weight in people with IDDM is positively associated with blood pressure in both men and women. Cholesterol increased significantly with body weight in men only, and fasting glucose increased significantly in women only. For both sexes, the leanest people had the highest mortality rates. Mortality rates in the four heaviest groups were generally not significantly different from each other. Adjustment for confounders, such as smoking and proteinuria, and for factors that may be on

Table 2—*Relative risks for all deaths according to BMI by sex in patients with IDDM*

	Category of BMI (kg/m²)				
	<20	20 to <22	22 to <24	24 to <26	26+
Men					
Number of deaths	26	26	34	28	33
RR1	2.64 (1.59–4.38)*	1.28 (0.81–2.05)	1.00	1.20 (0.76–1.89)	1.63 (1.03–2.58)†
RR2	2.14 (1.27–3.60)‡	1.34 (0.83–2.16)	1.00	1.11 (0.70–1.76)	1.56 (0.98–2.49)
RR3	2.53 (1.50–4.26)*	1.24 (0.77–2.02)	1.00	1.02 (0.64–1.62)	1.52 (0.98–2.37)
Women					
Number of deaths	12	11	28	14	35
RR1	1.54 (0.77–3.06)	0.84 (0.45–1.59)	1.00	0.96 (0.54–1.73)	0.97 (0.60–1.58)
RR2	1.94 (0.96–3.94)	0.83 (0.44–1.57)	1.00	0.90 (0.50–1.64)	0.94 (0.58–1.54)
RR3	2.21 (1.08–4.51)‖	0.94 (0.50–1.78)	1.00	0.84 (0.46–1.53)	0.88 (0.54–1.43)

Data are relative risks (RRs) (95% CI): 1, adjusted for age, duration, and center; 2, adjusted for age, duration, center, smoking, and proteinuria; 3, adjusted for age, duration, center, smoking, proteinuria, systolic blood pressure, and cholesterol. *$P < 0.001$; †$P = 0.04$; ‡$P = 0.004$; §$P = 0.001$; ‖$P = 0.03$.

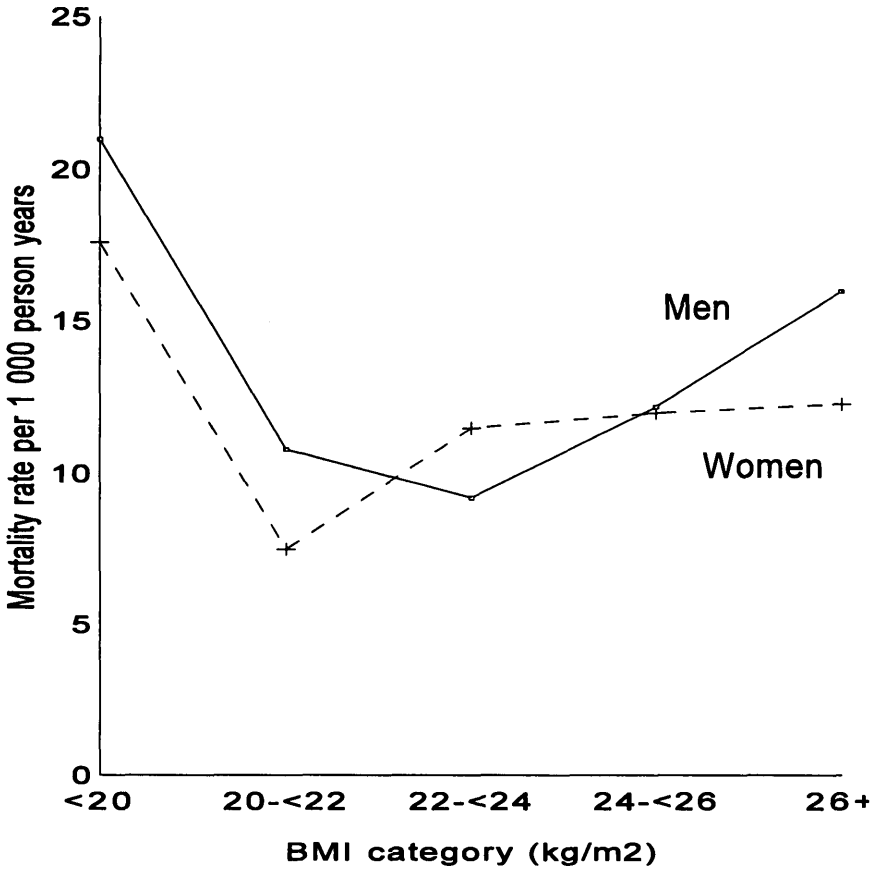

Figure 1—*All-cause mortality rates by BMI in people with IDDM (adjusted for age and duration of diabetes). Men: χ^2 for trend 0.01, P = 0.9; women: χ^2 for trend 0.04, P = 0.8.*

the causal pathway between body weight and mortality, such as blood pressure and cholesterol, did not significantly alter our findings. We therefore show that higher levels of BMI are not associated with an increased risk of mortality. These findings provide important evidence for the debate surrounding the risks and benefits of efforts to improve glycemic control in people with IDDM.

Intensive glycemic control has been shown to result in an average weight gain of 5 kg (1), but the reasons for this are not clear. Some studies suggest that intensive insulin therapy may alter eating habits (17) or that metabolic rate is decreased (18). In the Diabetes Control and Complications Trial study, the leanest subjects with the poorest initial control gained the most weight after achieving high-quality control (1). People with poor control are lean because they lose calories through glycosuria; improving control restores anabolism and, hence, results in weight gain. Thus, it is those subjects who have the most to gain from tight control, in terms of avoiding microvascular complications, who gain the most weight. Disease severity may therefore be the explanation for the high mortality rates observed in the leanest group.

An alternative explanation is that the leanest groups are already unwell and have lost weight before examination. Thus, the exclusion of all deaths in the 1st year of follow-up has not adequately accounted for this bias. This suggestion is supported by the high prevalence of proteinuria and, in men, the high prevalence of current smokers in the leanest group. Adjustment for smoking and proteinuria partially attenuated the relationship between obesity and mortality, but the high mortality rates in the leanest group persisted. Exclusion of deaths in the first 3 years of follow-up also attenuated this relationship, supporting our hypothesis that the high death rates observed in the leanest group may be partially due to early disease resulting in weight loss.

Ideally, mortality rates by weight gain that is due to improvements in glycemic control should be examined. The mortality follow-up of studies reporting the association between weight gain and glycemic control will take several years, however, and an assessment of the possible effects of weight differences on mortality is urgently needed to inform health care policy. The group of subjects in the WHO MSVDD study is one cohort in which this question can be addressed. However, in this study, people in the most obese categories are not obese simply because their glycemic control is better; in fact, our data suggest that, at least in women, control may be worse. This poor-control factor alone should result in an increased mortality risk in the most obese groups. Despite this, we still find little difference in mortality across the heaviest four categories. Greater body weight may, therefore, have a protective effect on mortality, and we may have overestimated the effects of tight-control–related obesity on mortality.

In conclusion, we show that body weight in people with IDDM is positively related to higher blood pressure and serum cholesterol and that this relationship is stronger for men than for women. Death rates are highest in the leanest category in both sexes, but thereafter, increasing weight appears to have little relationship with mortality. The reasons for the high mortality rates in the leanest group are unclear, but may be due to poorer glycemic control in this group, higher smoking rates (at least in men), and the existence of preclinical illness leading to wasting. We conclude that the increase in body weight associated with a tightening in glycemic control confers little disadvantage in terms of a change in

risk factors or, more importantly, mortality and that concerns about weight gain should not deter those attempting to reduce the risk of diabetes complications by striving for strict glycemic control.

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APPENDIX— Participating centers and investigators in the WHO MSVDD—London, U.K.: J.H. Fuller, R.J. Jarrett, H. Keen, N.J. Morrish, and P. J. Watkins; Bern, Switzerland: A. Teuscher, T. Teuscher, P.P. Studer, and P. Diem; Warsaw, Poland: A. Czyzyk, D. Janeczko, and J. Kopczynski; Berlin, Germany: M. Raskovic, V. Schliack, and K. P. Ratzmann; Zagreb, Croatia: I. Aganovic, A. Skrabolo, A. Stavljenic, and G. Roglic; Hong Kong: R.T.T. Young, K. Lam, and J. Ma; Tokyo, Japan: K. Kosaka and E. Miki; Havana, Cuba: O. Mateo de Acosta, S. Amaro, O. Diaz, M. Hang, X. Quesda, and A. Hernandez Yero; Oklahoma City, OK: E. Lee; Phoenix, AZ: P.H. Bennett, D.J. Pettitt, and R.G. Nelson.

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