Exercise Capacity and Body Mass as Predictors of Mortality Among Male Veterans With Type 2 Diabetes

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OBJECTIVE — To demonstrate the relation of exercise capacity and BMI to mortality in a population of male veterans with type 2 diabetes.

RESEARCH DESIGN AND METHODS — After excluding two underweight patients (BMI <18.5 kg/m^2), the study population comprised 831 consecutive patients with type 2 diabetes (mean age 61 ± 9 years) referred for exercise testing for clinical reasons between 1995 and 2006. Exercise capacity was determined from a maximal exercise test and measured in metabolic equivalents (METs). Patients were classified both according to BMI category (18.5–24.9, 25.0–29.9, and $\geq$30 kg/m^2) and by exercise capacity ($<$5.0 or $\geq$5.0 maximal METs). The association among exercise capacity, BMI, other clinical variables, and all-cause mortality was assessed by Cox proportional hazards. Study participants were followed for mortality up to 30 June 2006.

RESULTS — During a mean follow-up of 4.8 ± 3.0 years, 112 patients died, for an average annual mortality rate of 2.2%. Each 1-MET increase in exercise capacity conferred a 10% survival benefit (hazard ratio 0.90 [95% CI 0.82–0.98]; $P = 0.01$), but BMI was not significantly associated with mortality. After adjustment for age, ethnicity, examination year, BMI, presence of cardiovascular disease (CVD), and CVD risk factors, diabetic patients achieving $<$5 maximal METs were 70% more likely to die (1.70 [1.13–2.54]) than those achieving $\geq$5 maximal METs.

CONCLUSIONS — There was a strong inverse association between exercise capacity and mortality in this cohort of men with documented diabetes, and this relationship was independent of BMI.

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Individuals volunteering and qualifying for military service differ from the general population in several respects; most notably, they had to have met fitness and weight criteria at the time of their enlistment and must have maintained these levels for the duration of their service. For example, the maximum allowable weights for the various branches of service translate into a BMI of 25.9–29.9 kg/m^2 (1). Therefore, obesity, when present in a veteran patient population, must have developed after discharge, thus providing an opportunity to evaluate the risk of mortality associated with low fitness and obesity developing in later life. While obesity is a well-recognized risk factor for the development of type 2 diabetes (2), it is uncertain whether obesity is an independent mortality predictor in people already having the disease. Moreover, the association of fitness with mortality in patients with diabetes remains largely unexplored.

Recent reports have suggested that mortality risk in men with type 2 diabetes is independent of BMI after adjustment for fitness (3,4). Because this observation runs contrary to current clinical beliefs, we decided to explore this further using a subpopulation of male veterans with documented type 2 diabetes from our exercise testing database.

The primary aims of this study of male veterans with type 2 diabetes were to examine *1*) the independent risks of mortality associated with low fitness and adult-onset obesity and 2) the associations among fitness, BMI, and mortality.

RESEARCH DESIGN AND METHODS

— The Veterans Exercise Testing Study (VETS) is a prospective epidemiologic investigation of $>$7,000 veteran patients referred to two university-affiliated Veterans Affairs medical centers (Long Beach VA, from 1987 to 1991; Palo Alto VA, from 1992 to 2006). From this database, a total of 869 men were recognized as having type 2 diabetes. (Cases of type 2 diabetes could only be documented from 1995 onwards; hence, all participants in the current study were evaluated at the Palo Alto VA.) Of these, 36 subjects were excluded because of missing data on height, weight, or exercise capacity. In addition, two patients were excluded because they were underweight (BMI <18.5 kg/m^2). Therefore, participants for the present analysis were 831 men with type 2 diabetes who completed a baseline medical examination and maximal exercise test at least once at the Palo Alto VA Health Care System between 1995 and 2006. Type 2 diabetes was defined as a physician-diagnosed history of type 2 diabetes, treatment with an oral hypoglycemic agent, or a fasting plasma glucose level $\geq$7.0 mmol/l ($\geq$126 mg/dl) at baseline (5). Only two patients were identified as receiving insulin treatment at baseline. The study population consisted of 62% non-Hispanic whites, 15% Hispanics, and 14% African Americans who ranged in age from 23 to 88 years (average 61.3 ± 9.3). All subjects gave informed consent for participation in the study. Additional information on study methods and subject characteristics of this cohort have been published elsewhere (6,7).

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Abbreviations: ACLS, Aerobics Center Longitudinal Study; CVD, cardiovascular disease; MET, metabolic equivalent; VETS, Veterans Exercise Testing Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Mortality surveillance

Study participants were followed from their baseline examination until their death or until 30 June 2006. The California Health Department Service and Social Security Death Indexes were used to ascertain the vital status of each subject. Accuracy of deaths was reviewed by two clinicians blinded to exercise test results and confirmed using the Veterans Affairs computerized medical records. Thus, to our knowledge, no patients were lost to follow-up.

Clinical evaluation and exercise testing

Maximal exercise testing was performed using an individualized ramp protocol (8) on either a treadmill ($n = 780$) or an electromagnetically braked cycle ergometer ($n = 51$). Before ramp testing, patients completed a Veterans Specific Activity Questionnaire (VSAQ) to estimate their exercise capacity, which allowed most patients to reach maximal exercise within the recommended range of 8–12 min (9). A microcomputer automatically increased workload after an individualized walking speed (treadmill) or watts (cycle) was established and predicted values for maximal exercise capacity were entered. Immediately before the exercise test, height and weight were measured using standard procedures and BMI calculated as weight in kilograms divided by the square of height in meters. Subjects were assigned to categories of normal weight (BMI 18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese ($\geq$30.0 kg/m^2).

Blood pressure was recorded on alternate minutes throughout the test, and a 12-lead electrocardiogram was recorded each minute. The patient's subjective level of exertion was assessed by the Borg 6-20 scale (10). Standard clinical criteria for terminating the tests (e.g., fall in systolic blood pressure, ST-segment depression >2 mm, dangerous arrhythmias) were followed (11), but no heart rate or time limit was imposed, and a maximal effort was encouraged. Patients were discouraged from holding onto the handrails for support. Standardized equations were used to determine the calculated peak metabolic equivalents (METs) on the basis of treadmill speed and grade or cycle ergometer watts (11). Exercise capacity was expressed as the maximal MET value attained during the exercise test. Low fitness was defined as <5 METs according to the disability evaluation under Social Security (12) and as we have previously reported (6,13).

Statistical analysis

The statistical software NCSS (Kaysville, UT) was used for all statistical analyses. The mean and SD of each variable was calculated with participants categorized as survivors or decedents. Cox proportional hazards analyses were used to assess the independent and joint effects of fitness, BMI, and prevalent cardiovascular disease (CVD) and CVD risk factors at baseline with the risk of all-cause mortality.

To evaluate the relation of exercise capacity to mortality, <5 maximal METs was used as the cut point for low fitness and patients classified accordingly. Survival analysis was performed using Kaplan-Meier curves to compare mortality rates by <5 and ≥5 maximal METs and within each BMI category. Separate survival analyses were performed to compare mortality rates by BMI category for each fitness classification. The Cox-Mantel probability test was used to test for significant differences between groups, and $P < 0.05$ was accepted as statistically significant.

RESULTS — During a mean follow-up of 4.8 ± 3.0 years, 112 deaths were recorded. The general characteristics of the study population, grouped by survival status, are presented in Table 1. Approximately one-half of these diabetic patients were obese (BMI $\geq$30.0 kg/m^2), 74% had hypertension (diastolic blood pressure ≥90 mmHg and/or systolic blood pressure ≥140 mmHg), 49% had hypercholesterolemia (≥5.6 mmol/l), and 27% had CVD (history of myocardial infarction, congestive heart failure, stroke, and/or coronary bypass surgery). In general, surviving patients were younger and fitter, had a significantly higher BMI, included a lower percentage of current smokers, and had a lower prevalence of CVD and a higher prevalence of hypercholesterolemia than decedents. Low fitness (<5 METs) was less than half as prevalent among surviving patients compared with those who had died (17 vs. 39%, respectively; $P < 0.001$). Age-predicted mean maximum heart rates were 86 and 82% for survivors and decedents, respectively. The mean peak rating of perceived exertion (Borg 6-20 scale) was 17, which did not differ significantly between survival status categories, suggesting that the exercise test was maximal for most patients.

In a multivariate model after adjusting for age, ethnicity, and examination year (Table 2), each 1-MET increase in exercise capacity was associated with a 10% reduction in mortality (hazard ratio [HR] 0.90 [95% CI 0.82–0.98]). The HR for mortality associated with a low exercise capacity (<5 METs) was 1.80 (1.21–2.69), and after further adjustment for BMI, CVD, and CVD risk factors, the HR was 1.70 (1.13–2.54). The only other predictors of mortality were current smoking (1.93 [1.22–3.05]) and CVD (1.72 [1.17–2.52]). Conversely, BMI was not a significant predictor of mortality (0.98 [0.95–1.02] per BMI unit).

To address the effects of current smoking and preexisting CVD as confounding variables, we performed three separate analyses on the variables from Table 2 by *1*) adding current smoking to the adjusted HRs; *2*) calculating age-, ethnicity-, and examination year–adjusted HRs in the nonsmoking subgroup ($n = 698$); and *3*) calculating age-, ethnicity-, and examination year–adjusted HRs in the subgroup not having preexisting CVD ($n = 606$). Further adjustment for current smoking strengthened the CVD-mortality association (HR 1.85 [95% CI 1.25–2.72]), and compared with the main cohort, low fitness was a stronger mortality predictor in the subgroup not having preexisting CVD (1.97 [1.12–3.46]). Otherwise, the results were not appreciably affected.

To further assess associations among fitness, BMI, and mortality, we classified patients according to <5 and ≥5 maximal METs. We identified 167 patients achieving <5 maximal METs, which represented the least fit 20% of all participants. Kaplan-Meier survival analyses were performed to compare mortality rates by fitness classification for each BMI category (Fig. 1). Next, we generated Kaplan-Meier survival plots by BMI categories for each fitness classification (Fig. 2). Survival rates were higher among subjects with higher levels of fitness for each weight classification, but weight classification did not significantly affect mortality risk among patients with ≥5 maximal METs. However, among patients with low exercise capacity, overweight and obesity were protective.

CONCLUSIONS — Our main finding was that fitness is a powerful and independent predictor of mortality in men with diabetes, and this association is independent of BMI. We recently reported an obesity paradox (i.e., higher BMI is as-

Table 1—*Baseline characteristics of 831 men with type 2 diabetes grouped by survival status, VETS 1995–2006 participants*

	Total	Survived	Died	*P*
n (%)	831	719 (86.5)	112 (13.5)	
Age (years)	61.3 ± 9.3	60.5 ± 9.0	66.3 ± 10.0	<0.001
Age ≥65 years (%)	34.8	31.2	58.0	<0.001
Non-Hispanic white ethnicity (%)	61.7	61.4	63.4	0.69
BMI (kg/m^2)	31.1 ± 5.9	31.4 ± 6.0	29.2 ± 4.7	<0.001
BMI ≥35 kg/m^2 (%)	20.6	21.4	15.2	0.1
Resting heart rate (beats/min)	79.1 ± 26.7	79.6 ± 28.5	76.6 ± 12.3	0.28
Resting systolic BP (mmHg)	133.2 ± 18.8	132.7 ± 18.5	136.4 ± 20.6	0.08
Resting diastolic BP (mmHg)	79.1 ± 10.8	79.4 ± 10.7	77.1 ± 11.0	0.03
Cigarette smoking (%)				
Never	30.1	31.3	22.3	0.05
Past	53.9	53.7	55.4	0.74
Current	16.0	15.0	22.3	0.05
Hypertension (%)	73.8	74.2	71.4	0.53
Hypercholesterolemia (%)	49.0	50.5	39.3	0.03
Prevalent CVD (%)*	27.3	24.4	45.5	<0.001
Exercise capacity (METs)†	7.3 ± 2.8	7.5 ± 2.7	6.1 ± 2.9	<0.001
<5 METs (%)	20.3	17.3	39.3	<0.001
Peak systolic BP (mmHg)	176.3 ± 26.7	177.1 ± 26.4	170.4 ± 28.7	0.02
Peak heart rate (beats/min)	135.5 ± 21.9	137.0 ± 21.9	125.7 ± 19.2	<0.001
Perceived exertion (Borg scale)	16.7 ± 2.1	16.7 ± 2.1	16.9 ± 2.1	0.36

Data are means ± SD unless otherwise indicated. *CVD includes history of myocardial infarction, congestive heart failure, stroke, and/or coronary bypass surgery. †1 MET = 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ oxygen uptake; exercise capacity is the maximal METs achieved during the exercise test and is calculated from treadmill speed and grade or cycle ergometer watts using standard equations. BP, blood pressure.

sociated with lower mortality) among 6,876 patients from VETS and found that each 1-unit increment in BMI conferred a 3% survival benefit (14). However, BMI (as a continuous variable) was neither protective nor predictive in the current study of 831 male veterans with type 2 diabetes.

Among patients with type 2 diabetes, CVD accounts for >75% of total mortality (15), and hypertension, dyslipidemia, and smoking are each independent predictors of CVD mortality (16,17). However, the relation of obesity to CVD mortality remains controversial. For example, the UK Prospective Diabetes Study (UKPDS) reported that high BMI was not a major risk factor for coronary artery disease among patients with diabetes (18). We were not able to ascertain cause-specific mortality in the current study. Nevertheless, in our cohort of men with type 2 diabetes, those who were overweight or obese were not at greater risk of mortality than patients of normal weight, and this relationship was independent of fitness.

The Aerobics Center Longitudinal Study (ACLS) of men with diabetes found a positive association between BMI and all-cause mortality, but this association was not significant when adjusted for fitness (3). They also found that fitness was a powerful predictor of mortality, as we reported here. In contrast, however, we found an insignificant association between age-, ethnicity-, and examination year–adjusted BMI and mortality. This disparate finding is perhaps due to population differences, namely, that all our subjects were clinically referred, older (mean age 61.3 ± 9.3 vs. 49.3 ± 9.5 years in the ACLS), more ethnically diverse, and veterans. This latter factor—the "veteran effect"—may explain the different effects of BMI in the ACLS versus the current study. Veterans differ from other populations of patients in several respects. One of the most prominent differences is the meeting of selection criteria at the time of enlistment. These criteria include, among other things, minimum height requirements, maximum weight requirements, and exclusion of recruits having certain preexisting health problems. Consequently, individuals having obesity in early life are excluded from our population. It is noteworthy in this context that pediatric obesity has been shown

Table 2—*Age-, ethnicity-, and examination year–adjusted HRs of all-cause mortality according to exercise capacity, BMI, and other clinical variables for 831 men with diabetes, VETS 1995–2006*

Variable	HR (95% CI)	*P*
Maximal METs (per 1-MET increment)*	0.90 (0.82–0.98)	0.014
BMI (per 1-unit increment)	0.98 (0.94–1.02)	0.27
Hypertension	1.03 (0.69–1.57)	0.86
Hypercholesterolemia	1.07 (0.73–1.57)	0.74
Smoking		
Current	1.93 (1.22–3.05)	0.005
Past	0.79 (0.55–1.16)	0.24
CVD†	1.72 (1.17–2.52)	0.006
Low fitness (<5 maximal METs)	1.80 (1.21–2.69)	0.004

*1 MET = 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ oxygen uptake; exercise capacity is maximal METs achieved during the exercise test and is calculated from treadmill speed and grade or cycle ergometer watts using standard equations. †CVD includes history of myocardial infarction, congestive heart failure, stroke, and/or coronary bypass surgery.

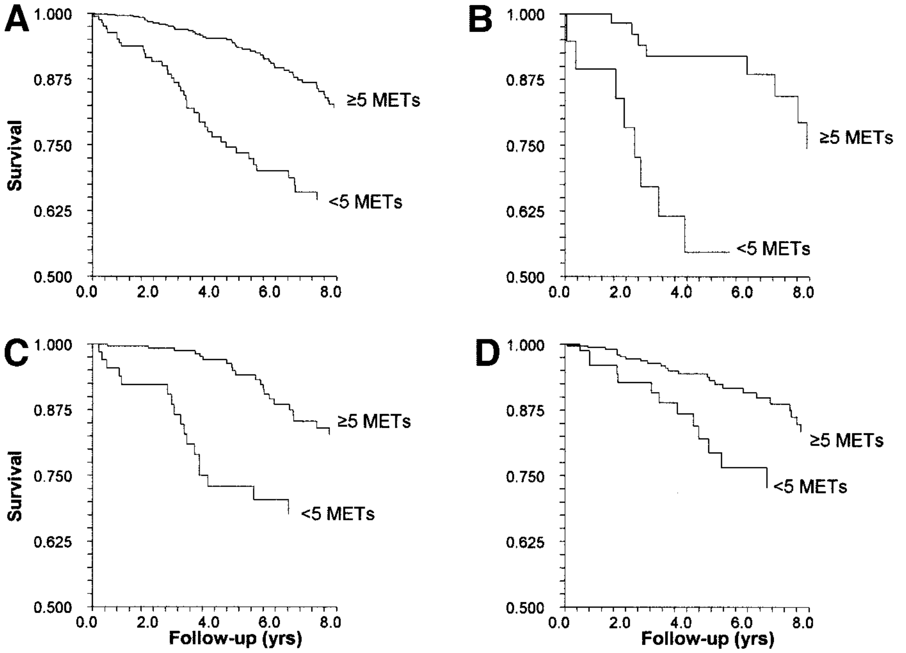

Figure 1— A: *Survival curves illustrating the probability of surviving with different levels of exercise capacity from 831 men with type 2 diabetes (<5 METs vs. ≥5 METs, P < 0.001).* B: *Survival curves in 78 normal-weight (BMI 18.5–24.9 kg/m²) men with type 2 diabetes (<5 METs vs. ≥5 METs, P < 0.001).* C: *Survival curves in 330 overweight (BMI 25.0–29.9 kg/m²) men with type 2 diabetes (<5 METs vs. ≥5 METs, P < 0.01).* D: *Survival curves in 423 obese (BMI ≥30.0 kg/m²) men with type 2 diabetes (<5 METs vs. ≥5 METs, P < 0.05). The area under the survival curves is the total life expectancy for populations with an exercise capacity of <5 METs or an exercise capacity of ≥5 METs (VETS 1995–2006).*

to have a greater impact on disease outcomes than obesity that develops in later life. For example, Barker et al. (19) recently examined the effects of birth weight and childhood growth rates on subsequent disease risk in Finnish men and women. They reported that the rate of childhood gain in BMI between 2 and 11 years of age was strongly related to the risk of coronary events and insulin resistance in later life. Such individuals would be excluded from the veteran population by reason of weight. Finally, the influence of self-selection in our population must be considered. Individuals volunteering and qualifying for military service may be more likely to be predisposed toward physical fitness or have other health attributes than those avoiding military service.

We found that the inability to achieve 5 maximal METs was as powerful a mortality predictor as CVD and smoking and was a stronger predictor of mortality than more traditional risk factors, such as hypercholesterolemia and hypertension. When considering BMI as a categorical variable, the probability of surviving was significantly lower among patients of normal weight (BMI 18.5–24.9 kg/m²) compared with obese (≥30.0 kg/m²) patients ($P < 0.01$). However, we insert a note of caution here, as the normal-weight group comprised only 9% of the study population. Regardless, among the subgroup with low fitness (representing 20% of the cohort), those classified as overweight (25.0–29.9 kg/m²) or obese (≥30.0 kg/m²) had improved survival compared with those of normal weight (18.5–24.9 kg/m²). An obesity paradox was therefore evident among diabetic veterans with low fitness but not among those with higher levels of fitness.

Our study has several strengths, including *1*) all subjects underwent an extensive physical examination, which provides thorough information on the presence or absence of baseline disease; *2*) cardiorespiratory fitness was determined by maximal exercise testing; and *3*) our sample size consisted of >800 men with documented type 2 diabetes with an average follow-up of nearly 5 years. However, a lack of information on oral hypoglycemic medication use (e.g., metformin) limits this investigation. Another limitation of our study is that it included only men who had prior military service

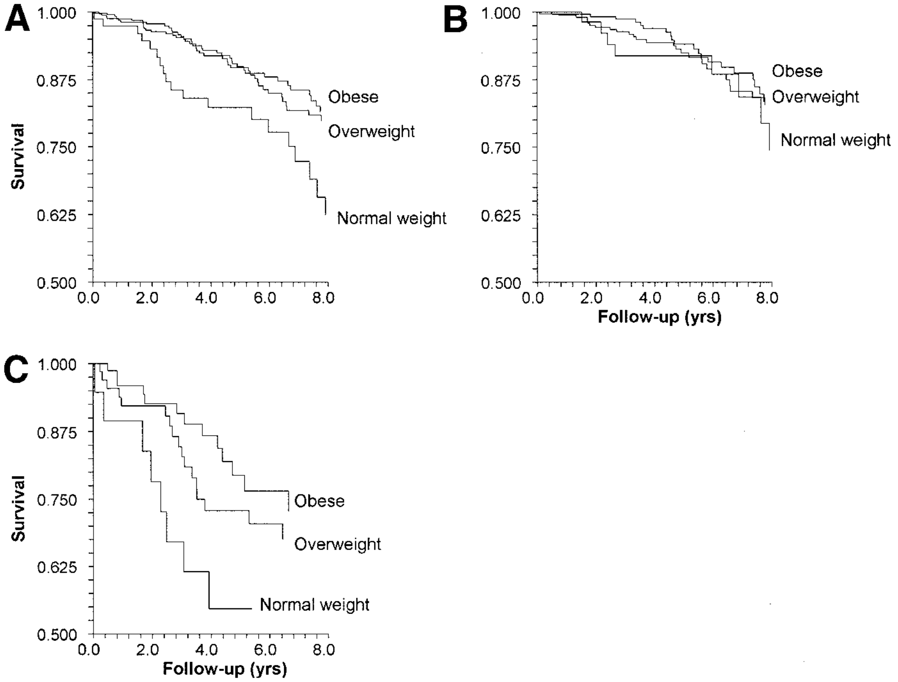

Figure 2— A: *Survival curves illustrating the probability of surviving with different weight categories from 831 men with type 2 diabetes (overweight vs. normal weight, P = 0.18; obese vs. normal weight, P < 0.01).* B: *Survival curves in 664 men with type 2 diabetes with an exercise capacity of ≥5 METs (overweight vs. normal weight, P = 0.9; obese vs. normal weight, P = 0.56).* C: *Survival curves in 167 men with type 2 diabetes with an exercise capacity of <5 METs (overweight vs. normal weight, P < 0.05; obese vs. normal weight, P < 0.01). The area under the survival curves is the total life expectancy for normal weight (BMI 18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), or obese (≥30.0 kg/m²) populations (VETS 1995–2006).*

and were referred for exercise testing for clinical reasons. Thus, we evaluated survival in the context of a clinical population, many of whom were limited by symptoms, medications, and other factors related to CVD. Any effort to predict mortality by using fitness, BMI, or clinical or demographic data should be considered population specific. Therefore, our results may not apply to more general or healthier populations, and while these results may urge exercise and increased fitness as accepted clinical treatment for type 2 diabetes, long-term effects of exercise and fitness are virtually unknown. In addition, although BMI is the most commonly used method to determine obesity status, it is not the optimal measure (20). Finally, since we only have baseline data on weight, exercise capacity, and other exposures, we do not know whether changes in any of these variables occurred during follow-up or how this might have influenced the results.

In summary, we observed a strong inverse association between fitness and mortality in this cohort of men with documented diabetes, and this relationship was independent of BMI. These results suggest that more attention should be focused on increasing physical activity and fitness in overweight/obese patients with type 2 diabetes. Accordingly, the benefits associated with increased fitness—regardless of whether weight loss is achieved—should be stressed.

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