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Brief report

Cardiorespiratory fitness and mortality in diabetic men with and without cardiovascular disease

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ABSTRACT

We assessed joint associations of cardiorespiratory fitness and diabetes, cardiovascular disease (CVD), or both with all-cause. High-fitness eliminated mortality risk in diabetes ($P < 0.001$) and halved risk of death in diabetes/CVD ($P < 0.001$). Fitness was a potent effect modifier in the association of diabetes and CVD to mortality.

1. Introduction

The lifetime risk of cardiovascular disease (CVD) is higher for individuals with diabetes [1,2]. Higher cardiorespiratory fitness (fitness) attenuates the mortality risk associated with CVD[3] and diabetes [4,5]. Yet information on the influence of fitness on mortality in patients having both diabetes and CVD remains largely unexplored.

A previous report from the Veterans Exercise Testing Study (VETS) provided compelling evidence that moderate to high levels of fitness can reduce all-cause mortality risk in diabetic men [6]. This report, however, did not specifically examine the subgroup of diabetic patients with CVD, nor did it include a comparison group of men without diabetes and CVD. Therefore, we aim to quantify the all-cause mortality risks associated with various combinations of fitness level and diabetes, CVD and diabetes/CVD in a clinical cohort of male veterans referred for exercise testing.

2. Research design and methods

The Veterans Exercise Testing Study (VETS) is a prospective epidemiologic investigation of more than 9000 veteran

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patients (3% women) referred to two university-affiliated Veterans Affairs medical centers (Long Beach, from 1987 to 1991; Palo Alto, from 1992 to the present). From this database, a total of 7775 men were evaluated for inclusion into this study. We excluded 175 subjects because of missing data on height, weight or exercise capacity; and another 51 underweight patients (BMI < 18.5 kg/m^2). Therefore, participants for the present analysis were 7549 men who completed a baseline medical examination and maximal exercise test during 1987–2003. All subjects gave informed written consent for participation in the study. Additional information on study methods and subject characteristics of this cohort has been published elsewhere [7].

Height and weight were measured using standard procedures and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Maximal exercise testing was performed using an individualized ramp protocol as previously described [8]. We estimated maximal metabolic equivalents (METs, 1 MET = 3.5 ml O_2 uptake kg^{-1} min^{-1}) from final treadmill speed and grade using standard equations [9]. Subjects with diabetes included those with type 1 or type 2 diabetes determined according to the American Diabetes Association diagnosis and classification criteria [10]. Patients classified as having CVD included those with a history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, stroke, and/or peripheral vascular disease. We defined low, moderate, and high-fitness as <5, 5–10, and >10 METs, respectively, as in previous VETS reports [3,7]. Subjects were also classified according to diabetes/CVD status (neither, diabetes, CVD, and both), resulting in 12 combined disease status/fitness groups. The statistical software Number Crunching Statistical Software (Kaysville, UT) was used for all statistical analyses. Participants were followed for at least 1 year from their baseline examination until their death or until 30 December, 2004. The California Health Department Service and Social Security Death Indices were used to ascertain the vital status of each subject. Cox proportional hazards analyses were used to assess the joint effects of fitness and diabetes and CVD status at baseline with the risk of all-cause mortality. We selected no diabetes/no CVD and high-fitness (N = 1229) as the reference group and calculated hazard ratios (HRs) of all-cause mortality for the remaining 11 disease status-fitness groups. Covariates included age (years), ethnicity (non-Hispanic White, African-American, Hispanic, Asian-Pacific Islander, or unknown), currently smoking (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no) and BMI (kg/m^2). We used ANOVA to compare means for continuous variables and X^2 for categorical variables. All P values are 2-sided and $P < 0.05$ was regarded as statistically significant.

3. Results

We recorded 1637 deaths during a mean follow-up of 8.1 ± 4.7 years. The study population consisted of 74% non-Hispanic Whites, 9.2% Hispanics and 11.5% African-Americans, who ranged in age from 21 to 93 years (mean [SD] 59 [±11]). In general, subjects with neither diabetes nor CVD were younger, more likely to have high-fitness, less likely to have hypertension, but as likely to have hypercholesterolemia as those patients with diabetes, CVD or both (Table 1). Compared to the reference group, adjusted hazard ratios (HRs) (95% confidence intervals) for low-, moderate-, and high-fitness, respectively, were: 3.79 (2.08–6.90), 2.42 (1.54–3.82), and 0.95 (0.35–2.61) in diabetes; 4.62 (3.53–6.05), 2.83 (2.20–3.64), and 1.36 (1.00–1.85) in CVD; and 5.17 (3.62–7.39), 3.72 (2.68–5.16), and 2.60 (1.34–5.05)

Table 1 – Baseline characteristics according to disease status among 7549 men in the Veterans Exercise Testing Study, 1987–2003.

	Diabetes/CVD status				
	Neither (N = 3121)	Diabetes (N = 434)	CVD (N = 3496)	Both (N = 498)	P value
Age (years)	55.8 ± 11.9	58.5 ± 9.7	61.2 ± 10.3	62.4 ± 9.1	<0.001
Non-Hispanic White (%)	72.6	55.5	77.5	67.8	<0.001
BMI (kg/m^2)	28.5 ± 4.9	30.6 ± 5.7	27.8 ± 4.8	29.5 ± 5.2	<0.001
Fitness groups (%)					
Low-fit (<5 METs)	9.1	14.7	21.5	28.7	<0.001
Moderate-fit (5–10 METs)	51.5	66.1	58.9	58.2	<0.001
High-fit (>10 METs)	39.4	19.1	19.7	13.1	<0.001
Fitness, METs	9.5 ± 3.6	7.6 ± 2.9	7.6 ± 3.4	6.6 ± 3.0	<0.001
Blood pressure (mmHg)					
Systolic	131.7 ± 18.8	134.7 ± 20.1	133.7 ± 21.1	136.9 ± 20.7	0.001
Diastolic	82.8 ± 11.4	80.1 ± 10.8	81.5 ± 11.2	79.8 ± 11.9	<0.001
[a]Hypertension (%)	42.6	71.7	51.0	68.3	<0.001
Currently smoking (%)	29.6	23.7	30.5	19.9	<0.001
[b]Hypercholesterolemia (%)	30.2	39.6	30.9	38.2	<0.001

Data shown are mean ± SD unless otherwise specified. BMI, body mass index; METs, maximal metabolic equivalents achieved during the treadmill test; CVD, cardiovascular disease.
[a] History of physician diagnosed high cholesterol or measured fasting total cholesterol ≥ 220 mg/dL (5.70 mmol/L).
[b] History of physician diagnosed hypertension or measured resting systolic blood pressure ≥ 140 or resting diastolic blood pressure ≥ 90 mmHg.

Table 2 – Fitness level and diabetes/CVD status stratified HRs (95% CI) for all-cause mortality among 7549 men in the Veterans Exercise Testing Study, 1987–2003.

Fitness level	CVD/diabetes status	N	Deaths, N (%)	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)
High (>10 METs)	Neither	1229	71 (6)	1 [Ref.]	1 [Ref.]
	Diabetes	83	4 (5)	0.93 (0.34–2.56)	0.95 (0.35–2.61)
	CVD	688	97 (14)	1.40 (1.03–1.90)	1.36 (1.00–1.85)
	Both	65	10 (15)	2.49 (1.28–4.83)	2.60 (1.34–5.05)
Moderate (5–10 METs)	Neither	1607	214 (13)	1.73 (1.32–2.28)	1.80 (1.37–2.37)
	Diabetes	287	26 (9)	2.13 (1.36–3.34)	2.42 (1.54–3.82)
	CVD	2058	652 (32)	2.81 (2.19–3.62)	2.83 (2.20–3.64)
	Both	290	79 (27)	3.49 (2.52–4.83)	3.72 (2.68–5.16)
Low (<5 METs)	Neither	285	69 (25)	3.17 (2.26–4.46)	3.25 (2.31–4.59)
	Diabetes	64	13 (20)	3.53 (1.94–6.41)	3.79 (2.08–6.90)
	CVD	750	343 (46)	4.55 (3.48–5.95)	4.62 (3.53–6.05)
	Both	143	59 (41)	4.92 (3.46–6.99)	5.17 (3.62–7.39)

BMI, body mass index; METs, maximal metabolic equivalents achieved during the treadmill test; CVD, cardiovascular disease.
[a] The multivariate hazard ratio (HR) was calculated using Cox proportional hazards models adjusted for age, ethnicity, smoking, hypertension, hypercholesterolemia and BMI (entered as a continuous variable).

in diabetes/CVD (Table 2). Within disease group comparisons revealed that, relative to low-fit, mortality risks for high-fit patients were 50% lower for diabetes–CVD, nearly nullified (92%) for CVD, and completely nullified (100%) for diabetes (Table 2).

4. Discussion

Since objective measures of fitness from clinical exercise testing are not readily available, data on the joint associations of fitness and disease status to mortality are sparse. In the present study we observed a steep, inverse association between fitness and all-cause mortality that varied by disease status. We know of no previously published study that has specifically evaluated combined associations of fitness (as measured from standard exercise testing) and both diabetes and CVD with mortality.

Among the common comorbidities of diabetes, CVD is by far the most serious and costly [11]. Our results indicate complex associations of diabetes, CVD, and fitness to mortality. In terms of mortality risk reduction, diabetes was the most responsive, and diabetes/CVD the least responsive, to higher levels of fitness. While the mechanisms behind better survival with higher fitness level are not fully understood, high-fitness suggests better myocardial function [12], and enhanced endothelial or smooth muscle control of vascular resistance [13].

Our findings are limited by the selection procedures employed. Participants were all male U.S. veterans referred to exercise testing for clinical reasons. Veterans are different from other populations in that they have to meet military recruiting standards for health and fitness. Therefore, the findings may not generalize to more diverse populations.

In summary, higher levels of fitness reduced the mortality risk associated with diabetes, CVD, and diabetes/CVD. These results underscore the importance of preserving or improving fitness as a primary strategy to increase longevity in such individuals.

Conflict of interest

There are no conflicts of interest.

Contributions

All authors had access to the data and a role in writing the manuscript.

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