Fitness, Body Habitus, and the Risk of Incident Type 2 Diabetes Mellitus in Korean Men

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The relative contributions of cardiorespiratory fitness (CRF) and body habitus to predict incident type 2 diabetes mellitus (T2DM) remain unclear. We prospectively investigated the relation of CRF and body habitus on the risk of developing T2DM in men. Participants included 3,770 apparently healthy men who initially presented without baseline evidence of diabetes, cardiovascular disease, and hypertension. Participants were divided into 3 groups as normal weight (18.5 to 24.9 kg/m^2), obese I (25.0 to 29.9 kg/m^2), and obese II (≥30.0 kg/m^2). CRF was directly measured by peak oxygen uptake (VO_{2peak}) and categorized into unfit and fit cohorts based on the median value of age-specific VO_{2peak}. Diabetes was defined as a glycated hemoglobin >6.5% and/or a fasting glucose >126 mg/dl at baseline and follow-up examinations. During a median follow-up of 5 years, 170 men (4.5%) developed diabetes. After adjusting for age and fasting glucose, the relative risk and 95% confidence interval (CI) for incident T2DM were 1.52 (95% CI 1.11 to 2.07) for obese I and 3.11 (95% CI 1.35 to 7.16) for obese II versus normal weight and 0.69 (95% CI 0.51 to 0.95) for fit versus unfit. However, these associations were no longer statistically significant after adjusting for potential confounders with VO_{2peak} (1.32; 95% CI 0.96 to 1.83 for obese I and 1.61, 95% CI 0.64 to 4.06 for obese II vs normal weight) or body mass index (0.75, 95% CI 0.54 to 1.05 for fit vs unfit). In the joint analysis, obese-unfit men had 1.81 times (95% CI 1.22 to 2.69) greater risk of incident T2DM, but obese-fit men were not at increased risk of incident T2DM (0.95, 95% CI 0.57 to 1.58) compared with fit-normal weight men. In conclusion, these results suggest that both CRF and obesity predict the incidence of T2DM independent of potential confounders; however, CRF appears to attenuate the risk of developing diabetes in obese men. **(Am J Cardiol 2016;117:585−589)**

Cardiorespiratory fitness (CRF), a physiological biomarker of cardiorespiratory and muscular system integrity, which is highly reflective of habitual physical activity,[1] is more strongly related to varied health outcomes than self-reported physical activity.[2,3] For clinical purposes, CRF should be reported as the highest or peak-attained oxygen uptake (VO_{2peak}) during maximal or symptom-limited exercise testing.[3,4] Numerous studies suggest that CRF is inversely associated with insulin resistance,[5] a possible precursor of diabetes. The relative influence of CRF on insulin resistance is dampened when controlling for adiposity[6]; however, these associations require additional clarification.[7] Accordingly, it appears that CRF may attenuate the risk of incident type 2 diabetes mellitus (T2DM) in obese subjects but that it does not completely eliminate the increased risk associated with obesity.[8,9] Although CRF may modify the relation between obesity and the risk of associated adverse cardiometabolic outcomes,[2,7,10] its potential impact on the incidence of T2DM in obesity remains controversial.[9,11−13] These studies did not adjust for baseline fasting glucose levels, an important confounding variable in diabetes cohorts, or directly measure VO_{2peak}, an objective index of CRF. Other investigations identified diabetes cases using only self-reported data,[14] which may have also contributed to the inconsistencies in these publications. In this study, we investigated the individual and combined associations of CRF and obesity with the development of T2DM in men, adjusting for potential confounders, including fasting glucose levels.

Methods

Our study participants included 5,616 men who participated in 2 general health examinations from 1998 to 2009 at the Samsung Medical Center, Seoul, South Korea. Of these participants, men who had hypertension, T2DM, or a history of cardiovascular disease and those who were taking antihypertensive medications and/or oral hypoglycemic agents at baseline were excluded. Further exclusions included subjects whose relevant blood markers (glucose and glycated hemoglobin A1c) and CRF, determined during cardiopulmonary exercise testing, were not measured at

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See page 588 for disclosure information.

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Table 1
Baseline characteristics of participants with and without type 2 diabetes mellitus at follow-up (n = 3,770)

Variable	Diabetes Mellitus		P value
	No (n=3600)	Yes (n=170)	
Age (years)	47.7±6.3	48.9±5.9	0.012
Body mass index (kg/m^2)	24.3±2.4	25.2±2.6	<0.001
Current smokers	26.2%	18.8%	0.039
Alcohol consumption (≥ 3 day/week)	3.4%	8.2%	0.003
Resting heart rate (bpm)	62.6±8.5	62.5±7.9	0.834
Systolic blood pressure (mmHg)	116.7±11.5	117.8±10.9	0.242
Diastolic blood pressure (mmHg)	74.9±8.5	75.6±8.1	0.304
Total cholesterol (mg/dl)	201.0±33.0	205.1±36.4	0.123
High density lipoprotein cholesterol (mg/dl)	49.6±11.6	46.8±11.6	0.003
Low density lipoprotein cholesterol (mg/dl)	126.4±30.7	127.9±33.1	0.549
Triglyceride (mg/dl)	147.2±81.2	173.9±82.9	<0.001
Glucose (mg/dl)	94.8±9.2	108.9±10.0	<0.001
Glycated hemoglobin A1c (%)	5.29±0.39	5.78±0.40	<0.001
Uric acid (mg/dl)	5.81±1.15	5.91±1.19	0.258
Peak oxygen uptake (ml/kg/min)	35.0±5.0	34.1±5.2	0.022

Data are presented as mean (SD) or percentage.

baseline. Additionally, we excluded 32 underweight participants (body mass index [BMI] <18.5 kg/m^2). Following these exclusions (n = 1,846), 3,770 participants (mean age 47 years; range 20 to 76 years) free of hypertension, cardiovascular disease, and T2DM, who underwent peak or symptom-limited cardiopulmonary exercise testing and whose blood glucose markers were measured at baseline, were included in the final analysis. Participants were followed from 1 year to 12 years (median 5.0 years) after the baseline examination. T2DM was determined by glycated hemoglobin (HbA1c) ≥6.5% and/or fasting plasma glucose ≥126 mg/dl or physician diagnosis at the second examination. Written informed consent was obtained from all participants before they undergo the health screening program, and the study was approved by the medical center institutional review board. Smoking habits (never, past, and current), alcohol consumption (none, ≥3 day/week), and related demographic/lifestyle information were evaluated through questionnaire. BMI was calculated as weight (kg) divided by height squared (m^2) and categorized into 3 groups as normal weight (18.5 to 24.9 kg/m^2), obese I (25.0 to 29.9 kg/m^2), and obese II (≥30.0 kg/m^2), based on the body habitus criteria for Asian-Pacific populations as designated by the World Health Organization Western Pacific Region.[15]

Blood samples were collected in the morning after a 12-hour overnight fast and analyzed by the hospital clinical laboratory. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were analyzed by enzymatic colorimetric and liquid-selective detergent methods, respectively, using a Hitachi 7600 (Hitachi Co., Tokyo, Japan) analyzer. Serum uric acid levels were measured with enzymatic colorimetric methods by a clinical chemistry autoanalyzer (Aeroset Abbot Lab, Abbott Park, Illinois). Fasting glucose and HbA1c were determined using the Hexokinase UV method (Hitachi-7600; Hitachi Co.) and high-performance liquid chromatographic method. Inter- and intra-assay coefficients of variation were <5% for all blood variables.

Blood pressure and heart rate at rest were measured after >5 minutes of quiet rest; the heart rate was obtained using a 12-lead electrocardiogram (Hewlett-Packard ECG M 1700A, Hewlett-Packard Corporation, Palo Alto, California) in the supine position. Blood pressure was measured using an automated blood pressure monitor (Dinamap PRO 100; GE Healthcare, Milwaukee, Wisconsin) in the seated position. Participants underwent peak or symptom-limited cardiopulmonary treadmill exercise testing using the conventional Bruce protocol.[16] End points for exercise testing included a rating of perceived exertion (6 to 20 scale) >17 (very hard) and/or a peak respiratory exchange ratio >1.15, achievement of >90% of age-predicted maximal heart rate, patient request because of volitional fatigue, the attainment of a systolic blood pressure >250 mm Hg, increasing chest discomfort, threatening arrhythmias, >1 mm of horizontal or downsloping ST-segment depression, or combinations thereof. CRF was directly measured by VO_{2peak} during peak or symptom-limited treadmill exercise testing (Jaeger Oxycon Delta; Erich Jaeger, Hoechberg, Germany). VO_{2peak} (Jaeger Oxycon Delta; Eric Jaeger) was defined as the highest or peak-attained oxygen consumption, expressed as ml/kg/min, recorded during the test, and categorized into a binary variable of unfit (<50%) and fit (>50%) based on the median value of VO_{2peak} in age/decade-specific percentiles as previously reported.[17]

Data are expressed as mean and SD for continuous variables and as proportions for categorical variables. Baseline variable comparisons between men with and without the development of T2DM were performed using independent Student's *t* test for continuous variables and chi-square tests for categorical variables. Cox proportional hazards regression with adjustment for confounding factors was used to determine the single or combined effect of obesity and CRF on the incidence of T2DM. Analyses were adjusted for age, fasting glucose, systolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, heart rate at rest, uric acid, smoking, alcohol consumption, and VO_{2peak} when related to obesity, using BMI criteria, or when related to CRF. The joint associations of obesity and CRF on the risk of incident T2DM were examined using combined groups. Participants were divided into 4 groups (fit-normal weight, unfit-normal weight, fit-obese, and unfit-obese) based on cross-classification of CRF and obesity status (combined obese I and obese II). Our reference group was the fit-normal weight cohort. All multiplicative interactions between obesity and CRF were tested. Statistical significance was set at $p < 0.05$. All tests for statistical significance were 2 sided. Analyses were conducted using the SPSS 21.0 (SPSS, Armonk, New York).

Results

During a median follow-up of 5 years, 170 of the 3,770 men (4.5%) developed T2DM. Men who developed T2DM had greater age, BMI, alcohol consumption, glucose, triglycerides, and glycosylated hemoglobin (HbA1c) levels but lower HDL cholesterol and VO_{2peak} (all $p < 0.05$) at