The "Obesity Paradox": Does It Persist Among Israeli Patients With Decompensated Heart Failure? A Subanalysis of the Heart Failure Survey in Israel (HFSIS)

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ABSTRACT

Background: Earlier studies among heart failure (HF) patients reported a paradox of reduced mortality rates in those with increased body mass index (BMI). Recently, however, it has been shown that obesity was not associated with better prognosis in certain groups. The aim of this study was to evaluate the "obesity paradox" among patients included in the Heart Failure Survey in Israel (HFSIS).

Methods and Results: Clinical, demographic, and laboratory characteristics of 2,323 patients hospitalized with a diagnosis of acute or decompensated chronic HF in 25 public Israeli hospitals between March 1 and April 30, 2003, were categorized by BMI as: normal weight (18.5−24.9 kg/m^2; n = 837), overweight (25.0−29.9 kg/m^2; n = 877), or obese (≥30.0 kg/m^2; n = 574), excluding 35 patients with BMI <18.5 kg/m^2. Survival over 15 months was inversely related to BMI category. Age-adjusted mortality hazard ratio (HR) was 0.95 (95% confidence interval [CI] 0.79−1.14) for overweight patients and 0.70 (95% CI 0.55−0.88) for obese patients compared with normal-weight patients. After further adjustment for gender, ejection fraction, New York Heart Association functional class, ischemic heart disease, diabetes, hypertension, dyslipidemia, renal function, and medications (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, spironolactone), obesity was associated with a nonsignificant HR of 0.79 (95% CI 0.59−1.05). Hypertension and dyslipidemia were also paradoxically associated with better survival in our model (HR 0.74, CI 0.59−0.92; and HR 0.77, CI 0.63−0.94; respectively; both $P < .05$).

Conclusions: Our study falls in line with the obesity paradox observation (in obese but not overweight patients) in a large survey of HF patients, although this finding was not statistically significant on multivariate adjustment analysis. (*J Cardiac Fail 2012;18:62−67*)

Key Words: Obesity paradox, reverse epidemiology, congestive heart failure.

Despite significant progress in the management of congestive heart failure (HF), the condition remains a major cause of morbidity and mortality and a leading cause for hospitalization among the elderly.[1] The lifetime risk of developing heart failure is ∼20% for all patients >40 years old.[2]

Obesity has reached epidemic proportions in developed countries. Obesity-associated cardiomyopathy has been associated with cardiac hypertrophy and both diastolic and systolic dysfunction.[3] The mechanism by which obesity predisposes to heart failure independently from other risk factors remains obscure. Despite the fact that obesity is associated with a doubling of the risk of developing heart failure,[4] once the disease is established, a paradoxic state develops whereby patients with the greatest body mass index (BMI) experience longer survival.[4−6] This has been demonstrated in numerous studies in patients with systolic dysfunction[9−14] and has been confirmed in patients with HF with preserved ejection fraction (EF).[15] Furthermore, it has been shown that other body composition parameters, including percent body fat and total fat,[7] as well as central obesity as determined by waist circumference[8] in addition to BMI, were independently associated with better survival in patients with systolic HF. However, 2 recent studies that

compared obese patients to matched nonobese and that used propensity-score analysis for obesity have cast doubt on this inverse association between obesity and mortality.[16,17]

Our objectives were to assess the "real-life" relationship between heart failure and mortality in a comprehensive survey performed in Israel, adjusting for demographic and clinical characteristics.

Methods

Patient Population

We analyzed data for 2,288 patients hospitalized with a clinical diagnosis of HF with available body mass index (BMI) data out of 4,102 consecutive patients enrolled in the national Heart Failure Survey in Israel (HFSIS). The design of this survey has already been extensively described.[18,19] In brief, the survey was conducted between March and April 2003 in 93 out of 98 internal medicine wards and 24 out of 25 cardiology departments from 25 out of 26 public hospitals in Israel. The criteria used for the diagnosis of HF were symptoms of HF (at rest or during exertion) and objective evidence of cardiac dysfunction at rest. Diagnosis of acute HF or exacerbation of chronic HF was determined by the attending physician based on history, clinical presentation (symptoms and physical examination), response to HF therapy, chest radiography, echocardiography, radionuclide studies, cardiac catheterization findings, and in-hospital course.

Variable Definition and Classification

BMI was calculated as the ratio between weight (kg) and squared height (m^2). Categories were defined as normal weight (18.5−24.9 kg/m^2; n = 837), overweight (25.0−29.9 kg/m^2; n = 877), and obese (≥30.0 kg/m^2; n = 574). Thirty-five patients (1.5%) with BMI <18.5 were excluded from the analysis, owing to the small number of patients in this group and because of the established poor prognosis associated with cachexia in HF.[20]

Glomerular filtration rate (GFR) was estimated using the formula derived by the Modification of Diet in Renal Disease (MDRD) study group in mL min^{-1} 1.73 m^{-2} body surface area and is calculated as: $186 \times$ (serum creatinine − 1.154) × (age − 0.203) where serum creatinine is measured in mg/dL and age in years.[21]

Patients were considered to be diabetic if diabetes mellitus (DM) was specified among the concomitant diagnoses, if fasting glucose was >125 mg/dL, or if they were treated for DM.

Hypertension was defined in accordance with the Joint National Committee criteria,[22] ie, repeated systolic blood pressure measurements >140 mm Hg or repeated diastolic blood pressure measurements >90 mm Hg.

Dyslipidemia was defined if reported as a cardiovascular risk factor or if any of the following criteria were met: total cholesterol (TC) >200 mg/dL low-density lipoprotein cholesterol (LDL-C) >130 mg/dL, high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, or triglycerides (TG) >150 mg/dL. Ischemic heart disease (IHD) was considered to be significant coronary artery disease per previous coronary angiography or history of myocardial infarction. Echocardiographic data were available for 1,944 patients (85%).

Mortality data up to 1.5 years from hospitalization were obtained from the Israeli population registry in July 2004 for 99% of the patients. Overall mortality was determined for 3 broad EF

categories: preserved (≥50%), moderately decreased (30−49%), and severely decreased (<30%).

Statistical Methods

Data were analyzed with SAS software version 8.2 (SAS Institute, Cary, North Carolina). Characteristics by BMI category are presented as frequencies or mean ± SD unless otherwise specified, and compared by χ^2 tests for categoric variables and t test for normally distributed continuous variables.

P measures the statistical significance for the comparison of variables among the 3 BMI categories. The cumulative probability of mortality by BMI categories was calculated with the Kaplan-Meier method. Curves were compared with the log-rank test.

Multivariate adjusted hazard ratios (HRs) were obtained using the Cox proportional hazard model including age, sex, EF, New York Heart Association (NYHA) functional class, IHD, DM, hypertension, dyslipidemia, renal function, and medications (angiotensin-converting enzyme inhibitor [ACEI]/angiotensin receptor blocker [ARB], β-blocker, spironolactone). The validity of the proportional hazard assumption was tested by running a model including time-dependent explanatory variables to test the assumption of no time-dependent effect. No significant deviation from the proportional hazard assumption was detected.

The predictive ability of the model was evaluated with the use of a C-statistic corresponding to the area under a receiver operating characteristic curve.[18] C-statistic was 0.63. Variable selection was based on clinical judgment (in the case of NYHA functional class, IHD, GFR, ACEI/ARB, and spironolactone) and univariate significant association (in the case of age, sex, EF, DM, hypertension, dyslipidemia, renal function, and β-blockers). Use of medication in the models refers to treatment before admission for the index event.

Furthermore, we examined the association between obesity and outcome in propensity-matched cohorts of HF patients with and without DM in our study. We matched 264 pairs of obese and nonobese patients with DM and 208 pairs of obese and nonobese patients without DM using a greedy match algorithm. We then calculated the mortality HR for obese patients compared with nonobese patients after multivariable adjustment (for age, sex, EF, IHD, hypertension, dyslipidemia, GFR, ACEI/ARB, β-blockers and spironolactone).

Results

Compared with normal-weight or overweight patients, a higher proportion of obese patients were female, younger, and had a higher prevalence of DM, hypertension, and dyslipidemia (Table 1). Atrial fibrillation and past ventricular tachycardia were more frequent among obese patients. IHD did not differ among the various BMI groups.

A higher proportion of patients with elevated BMI were treated before admission with aspirin, ARBs, statins, and diuretics than the normal-weight group, in which digoxin use was more prevalent (Table 2). Interventricular septum was thicker in obese patients, and left ventricular size and estimated systolic pulmonary artery pressure did not differ among the BMI groups.

Over a median follow-up period of 15.5 months (interquartile range 13.8−16.1), 610 patients died. By the end of the first follow-up year mortality rates were 26.8% in the normal-weight group, 22.9% among overweight