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The Obesity Paradox, Weight Loss, and Coronary Disease

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ABSTRACT

PURPOSE: Because obesity is a cardiovascular risk factor but is associated with a more favorable prognosis among cohorts of cardiac patients, we assessed this "obesity paradox" in overweight and obese patients with coronary heart disease enrolled in a cardiac rehabilitation and exercise training (CRET) program, making this assessment in patients classified as overweight/obese using both traditional body mass index (BMI) and percent body fat assessments. Additionally, we assessed the efficacy and safety of purposeful weight loss in overweight and obese coronary patients.

PATIENTS AND METHODS: We retrospectively studied 529 consecutive CRET patients following major coronary events before and after CRET, and compared baseline and post program data in 393 overweight and obese patients (body mass index [BMI] $\geq$25 kg/m^2) divided by median weight change (median = −1.5%; mean +2% vs −5%, respectively). In addition, we assessed 3-year total mortality in various baseline BMI categories as well as compared mortality in those with high baseline percent fat (>25% in men and >35% in women) versus those with low baseline fat.

RESULTS: Following CRET, the overweight and obese with greater weight loss had improvements in BMI (−5%; P <.0001), percent fat (−8%; P <.0001), peak oxygen consumption (+16%; P <.0001), low-density lipoprotein cholesterol (−5%; P <.02), high-density lipoprotein cholesterol (+10%; P <.0001), triglycerides (−17%; P <.0001), C-reactive protein (−40%; P <.0001), and fasting glucose (−4%; P = .02), as well as marked improvements in behavioral factors and quality-of-life scores. Those with lower weight loss had no significant improvements in percent fat, low-density lipoprotein cholesterol, triglycerides, C-reactive protein, and fasting glucose. During 3-year follow-up, overall mortality trended only slightly lower in those with baseline overweightness/obesity who had more weight loss (3.1% vs 5.1%; P = .30). However, total mortality was considerably lower in the baseline overweight/obese (BMI $\geq$25 kg/m^2) than in 136 CRET patients with baseline BMI <25 kg/m^2 (4.1% vs 13.2%; P <.001), as well as in those with high baseline fat compared with those with low fat (3.8% vs 10.6%; P <.01).

CONCLUSIONS: Purposeful weight loss with CRET in overweight/obese coronary patients is associated with only a nonsignificant trend for lower mortality but is characterized by marked improvements in obesity indices, exercise capacity, plasma lipids, and inflammation, as well as behavioral factors and quality of life. Although an "obesity paradox" exists using either baseline BMI or baseline percent fat criteria, these results support the safety and potential long-term benefits of purposeful weight loss in overweight and obese patients with coronary heart disease.
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KEYWORDS: Coronary heart disease, Exercise; Obesity; Rehabilitation

"The art of simplicity is a puzzle of complexity."
Doug Horton (1891-1968)

Obesity is currently the second leading cause of preventable death in the US, with the prevalence of overweightness, obesity, and severe obesity of 127 million, 60 million, and 9 million, respectively.[1] In fact, obesity may soon overtake cigarette smoking as the leading cause of preventable death in the US.[2] Although obesity may contribute to the risk of

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cardiovascular disease by adversely affecting plasma lipids, blood pressure, metabolic syndrome/insulin sensitivity/diabetes, and left ventricular hypertrophy,[2-4] the role of obesity as an independent risk factor for heart disease, including coronary heart disease, remains controversial.[4-6]

Although obesity may be a powerful cardiovascular disease risk factor, numerous studies have identified a strong paradox about obesity and subsequent prognosis, whereby obese subjects with cardiovascular disease demonstrated a clear survival advantage compared with their leaner cohorts.[2,6] This "obesity paradox" has been best recognized in patients with systolic heart failure,[2,6-10] but substantial data also have identified this paradox in other groups of cardiovascular disease patients, including those referred to echocardiography with preserved systolic function,[11] hypertensive patients,[12,13] and in very large cohorts with coronary heart disease.[4,6,14] It has been theorized by some investigators that at least part of the inconsistent relationship between obesity and clinical events, including mortality, may be due to the inaccurate diagnosis of obesity by the conventional body mass index (BMI) assessment, and defining obesity by other methods, including percent body fat, waist circumference, and waist/hip ratio may be more accurate.[15-19]

CLINICAL SIGNIFICANCE

- Although obesity is a cardiovascular risk factor in epidemiological studies, an "obesity paradox" exists in which obesity is associated with favorable prognosis among cohorts of cardiac patients.
- These data confirm this paradox using standard body mass index and percent body fat criteria.
- Despite this "obesity paradox," these data demonstrate the value and safety of purposeful weight loss among overweight/obese cohorts with established coronary heart disease.

Lifestyle changes, including modifying diet and increasing exercise capacity, remain a cornerstone in the treatment of coronary heart disease, and formal programs such as cardiac rehabilitation and exercise training (CRET) have been shown to markedly benefit coronary risk factors and overall morbidity and mortality in secondary coronary prevention.[20-35] Despite these proven benefits, only limited data are available on the benefits of this therapy in overweight and obese coronary patients.[4,36-38] Additionally, few data are known about whether an "obesity paradox" exists in coronary patients enrolled in CRET and whether purposeful weight loss would be beneficial or harmful on subsequent survival. In fact, the efficacy and safety of weight loss has been questioned, including in patients with established cardiovascular disease.[6,7,14,39,40]

The present study assessed 3 important clinical questions: whether an "obesity paradox" is present in coronary patients enrolled in CRET using the accepted standard of BMI in determining overweight/obesity; whether an "obesity paradox" is present using percent body fat in defining overweight/obesity; and does purposeful weight loss favorably or unfavorably impact coronary risk factors and survival in overweight/obese coronary patients enrolled in CRET?

METHODS

Patients

We retrospectively reviewed the case records of 529 consecutive patients with coronary heart disease (44% percutaneous intervention, 35% bypass surgery, and 30% myocardial infarction; some patients had more than 1 event) who completed a 3-month formal program of CRET between January 2000 and July 2005 to ascertain relevant anthropometric, lipid, clinical, and psychological data as previously described.[24,25,27-33,37] We have previously demonstrated that our patients who complete CRET are fairly similar to patients who are candidates for CRET programs and who have initial testing but do not attend the formal program.[27,32,33] In this present study, we specifically assessed the data in 393 overweight and obese patients (BMI $\geq$25 kg/m^2) and 136 patients with lower BMI ($<$25 kg/m^2). We also divided overweight and obese patients by median weight change (median -1.5%; mean $+2\%$ vs -5%, respectively) to determine the efficacy and safety of purposeful weight loss in overweight and obese patients with coronary heart disease. Because the World Health Organization has determined that the gold standard for obesity is percent body fat ($>$25% in men and $>$35% in women),[41] we further compared 214 patients with "low percent fat" compared with 315 patients with "high percent fat." All patients provided informed and written consent for the CRET program and the study was approved by the institutional review board of Ochsner Medical Center in New Orleans.

Protocol

Detailed components of the phase II, CRET program have been reviewed elsewhere.[24,25,27-33,37] In brief, most patients enter the program 2 to 6 weeks (mean 3 ± 3 weeks) after hospital discharge. Patients received individual and group counseling from a registered dietitian, and dietary management is recommended by national guidelines. Patients received formalized exercise instruction, met 3 times per week for 12 weeks for group exercise and educational sessions (total 36 educational and exercise sessions), and were encouraged to exercise on their own (between 1 and 3 times weekly) on non-rehabilitation days (compliance with the nonstructured program was not formally assessed). Patients' individual exercise recommendations were tailored to the anaerobic threshold as determined during cardiopulmonary stress testing.[42,43] Specific weight management guidance was given to those subjects identified as

being overweight or obese by either BMI or percent body fat methods, and these recommendations were reinforced during individual and group sessions by dietitians as well as other CRET staff (exercise physiologists and nurses). Educational classes were given with regards to all aspects of coronary risk, including hypertension, smoking cessation, diabetes, psychological risk factors, and weight management.

At baseline, fasting plasma lipids, glucose, high-sensitivity C-reactive protein (CRP), and percent body fat were assessed.[44] Body fat was assessed by the sum of the skinfold method using an average of 3 skin folds—thigh, chest, and abdomen in men; thigh, triceps, and supra-iliac in women. All measurements were made in the early morning before exercise. In addition, questionnaire data were obtained using the Kellner Symptom Questionnaire[45] to assess depression, anxiety, somatization, and hostility, and the MOS (Medical Outcomes Study) Short-Form 36 Questionnaire was used to assess overall quality of life, as described previously.[30-33] A lower score on the Kellner Symptom Questionnaire indicates a more favorable psychological trait, and a higher score on the MOS Short-Form 36 Questionnaire indicates a more favorable quality-of-life trait. Symptom-limited cardiopulmonary exercise testing was performed as previously described in detail.[42,43] All of the parameters were measured again within 1 week following the CRET program. Patients were followed for an average of over 3 years (mean 1295 ± 550 days; range 109-2199 days) to determine all-cause mortality (but not cause-specific mortality) assessed by the National Death Index.

Statistical Analysis

Statview software 5.0.1 (SAS Institute; Cary, NC) was used for statistical analysis. Means ± 1 SD or proportions for baseline risk factors were compared for all subgroups, and the significance of any differences between groups in means tested with the Student's *t* test; differences in proportions were tested with the chi-squared statistics. Baseline and post-CRET data were compared with paired *t* test. A value of $<.05$ was considered statistically significant. Actuarial survival analysis was used to compute cumulative hazard over time (Logrank; Mantel-Cox).

RESULTS

Baseline Characteristics

Baseline data describing patients with low and high BMI are demonstrated in Table 1. At baseline, patients with high BMI averaged to be 4 years younger ($P<.0001$), and this group had significantly higher levels of percent body fat ($P<.0001$), triglycerides ($P<.001$), fasting glucose ($P<.01$), and prevalence of diabetes ($P=.054$), and lower levels of high-density lipoprotein (HDL) cholesterol ($P<.0001$) compared with those with low BMI. Only 5 of the 529 patients were active smokers, including 3 in the low BMI group and 2 in the high BMI group. Likewise, Table 2 describes the baseline data in patients with low and high percent body fat. Patients with low percent fat, besides having lower body fat (by design) and BMI ($P<.0001$), had significantly lower triglycerides ($P=.039$), fasting glucose ($P<.01$), and hostility scores ($P=.033$), and higher levels of HDL cholesterol ($P=.014$) and peak oxygen consumption ($P=.023$) compared with those with high percent body fat, whereas other factors were statistically similar. Importantly, unlike the high BMI group who had slightly lower age than the low BMI group, the high percent fat group were younger by only 1.6 years ($P=.092$) compared with the low fat group.

Table 1 Baseline Characteristics of Coronary Patients Divided by Low and High Body Mass Index (BMI <25 kg/m^2 vs BMI ≥ 25 kg/m^2)

Characteristics	Low BMI (n = 136)	High BMI (n = 393)	*P* Value
Age, years	67.6 ± 10.6	63.2 ± 10.1	<.0001
% Female	22%	24%	.47
% Diabetes	13%	22%	.054
% hypertensive	30%	33%	.34
BMI, kg/m^2	22.9 ± 1.7	30.4 ± 4.4	<.0001
% Fat	24.1 ± 5.8	31.3 ± 7.8	<.0001
Ejection fraction %	52.4 ± 12.7	54.6 ± 4.4	<.06
Total cholesterol, mg/dL	166 ± 40.0	167±37	.76
Triglycerides, mg/dL	127 ± 56	156 ± 91	<.001
HDL cholesterol, mg/dL	46.1 ± 14.7	39.6 ± 11.7	<.0001
LDL cholesterol, mg/dL	95.3 ± 27.5	98.1 ± 38.2	.43
C-reactive protein, mg/dL	4.9 ± 10.8	5.8 ± 8.5	.33
Fasting glucose, mg/dL	103 ± 20	113 ± 32	<.01
Systolic blood pressure, mm Hg	126 ± 18	125 ± 20	.99
Diastolic blood pressure, mm Hg	73 ± 10	74 ± 11	.31
Peak oxygen consumption, mL/kg/min	16.3 ± 4.9	16.7 ± 5.3	.42
Anxiety, units	4.5 ± 5.1	4.0 ± 4.4	.29
Depression, units	3.5 ± 4.4	3.3 ± 3.9	.58
Somatization, units	6.9 ± 4.0	6.6 ± 3.9	.45
Hostility, units	2.1 ± 3.1	2.7 ± 3.6	.11
Quality of life, units	101 ± 18	103 ± 18	.20

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Among those patients with BMI ≥ 25 kg/m^2 who were divided by median weight change (median = 1.5%; mean +2% and −5% respectively) during CRET (Table 3), those with higher weight loss had slightly lower age ($P=.03$) but had higher baseline BMI ($P<.0001$), percent body fat ($P<.01$), and CRP ($P<.05$) compared with those with low weight loss.

Benefits of CRET

Following formal CRET programs, the overweight and obese patients who were less successful with weight loss (mean ± 2%; $P<.0001$) still had significant improvements in HDL cholesterol ($P<.0001$), peak oxygen consumption ($P<.0001$), behavioral characteristics (all $P<.001$), and quality of life ($P<.0001$), and had borderline improvement

Table 2 Baseline Characteristics of Coronary Patients with Low Percent Body Fat (≤25% in Men ≤35% in Women) and High Percent Body Fat (>25% in Men and >35% in Women)

Characteristics	Low Fat (n = 214)	High Fat (n = 315)	*P* Value
Age, years	65.3 ± 11.2	63.7 ± 9.8	.092
% Female	28%	27%	.97
% Diabetes	18%	22%	.40
% Hypertensive	36%	33%	.37
BMI, kg/m^2	22.4 ± 3.5	30.8 ± 4.9	<.0001
% Fat	23.6 ± 5.0	33.8 ± 6.1	<.0001
Ejection fraction %	53.1 ± 12.4	54.7 ± 11.2	.11
Total cholesterol, mg/dL	166 ± 39	168 ± 37	.54
Triglycerides, mg/dL	140 ± 73	156 ± 92	.039
HDL cholesterol, mg/dL	42.8 ± 14.7	40.0 ± 11.0	.014
LDL cholesterol, mg/dL	95 ± 30	98 ± 36	.26
C-reactive protein, mg/dL	4.8 ± 9.3	6.2 ± 9.3	.12
Fasting glucose, mg/dL	105 ± 22	113 ± 34	<.01
Systolic blood pressure, mm Hg	125 ± 21	125 ± 19	.92
Diastolic blood pressure, mm Hg	73 ± 10	74 ± 11	.17
Peak oxygen consumption, mL/kg/min	17.3 ± 5.2	16.2 ± 5.1	.023
Anxiety, units	4.1 ± 4.5	4.1 ± 4.7	.89
Depression, units	3.2 ± 4.0	3.5 ± 4.1	.54
Somatization, units	6.6 ± 3.7	6.6 ± 4.1	.89
Hostility, units	2.2 ± 3.0	2.8 ± 3.8	.033
Quality of life, units	102 ± 17	103 ± 18	.56

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

in triglycerides (−6%; $P = .08$). However, this group had no significant improvements in percent body fat, total cholesterol, low-density lipoprotein (LDL) cholesterol, CRP, or fasting glucose (Table 4).

On the other hand, the overweight and obese patients who were more successful with weight reduction (mean −5%; $P < .0001$) had more significant improvements in most of their coronary risk factors (Table 5). In this group, percent body fat improved by −8% ($P < .0001$), triglycerides −17% ($P < .0001$), HDL cholesterol +10% ($P < .0001$), LDL cholesterol −5% ($P < .03$), CRP −40% ($P < .0001$), fasting glucose −4% ($P < .03$), and peak oxygen consumption +16% ($P < .0001$), in addition to significant improvements in behavioral factors and quality of life (all $P < .001$).

Three-Year Mortality

During over 3 years of follow-up, all-cause mortality was strongly and negatively associated with baseline BMI (Figure 1). The highest mortality occurred in patients with baseline BMI <25 kg/m^2 (13.2%), versus only 1.8% in those with baseline BMI ≥35 kg/m^2. Only 6 patients in this cohort were underweight (BMI <18.5 kg/m^2) and during follow-up, 3 of these patients died (50% mortality). Excluding those patients with baseline BMI <18.5 kg/m^2 does not significantly reduce the significance of any of the major study's findings. In the entire group with baseline BMI <25 kg/m^2 versus those with baseline BMI ≥25 kg/m^2, mortality was 13.2% versus 4.1%, respectively (Figures 2A, 3A). Likewise, when patients were divided by baseline percent body fat (cutoff >25% in men and >35% in women), those with high body fat had significantly lower mortality (3.8% vs 10.6%, respectively; Figures 2B, 3B). Although mortality was relatively low in those with baseline BMI ≥25 kg/m^2, mortality trended slightly, but not significantly, lower in those with greater weight loss (3.1% vs 5.1%, respectively; $P = .30$; Figure 2C).

DISCUSSION

This study has several important and practical clinical findings. First, this study confirms the "obesity paradox" for the first time among patients enrolled in formal CRET programs, in that overweight and obese coronary patients by BMI criteria have more adverse baseline coronary risk profile yet have considerably lower overall mortality during follow-up. Second, even when coronary patients were di-

Table 3 Baseline Characteristics of Overweight and Obese Coronary Patients Divided by Median Weight Loss Following Cardiac Rehabilitation

Characteristics	Low Weight Loss* (n = 197)	High Weight Loss (n = 196)	*P* Value
Age, years	64.3 ± 9.8	62.1 ± 10.3	.035
% Female	21%	27%	.15
% Diabetes	21%	23%	.79
% Hypertensive	32%	34%	.83
BMI, kg/m^2	29.6 ± 4.0	31.2 ± 4.6	<.0001
% Fat	30.0 ± 7.2	33.4 ± 8.2	<.01
Ejection fraction %	54.5 ± 10.7	54.7 ± 11.1	.48
Total cholesterol, mg/dL	168 ± 35	166 ± 39	.66
Triglycerides, mg/dL	157 ± 89	155 ± 94	.80
HDL cholesterol, mg/dL	40.3 ± 11.6	39.0 ± 11.6	.25
LDL cholesterol, mg/dL	98.1 ± 36.1	98.2 ± 40.3	.99
C-reactive protein, mg/dL	4.9 ± 6.2	6.7 ± 10.3	.047
Systolic blood pressure, mm Hg	125 ± 19	127 ± 21	.97
Diastolic blood pressure, mm Hg	74 ± 10	74 ± 12	.91
Fasting glucose, mg/dL	112 ± 32	113 ± 32	.90
Peak oxygen consumption, mL/kg/min	16.4 ± 4.8	17.1 ± 5.6	.12
Anxiety, units	3.9 ± 4.4	4.1 ± 4.4	.73
Depression, units	3.4 ± 4.0	3.2 ± 3.8	.56
Somatization, units	6.5 ± 4.1	6.6 ± 3.7	.74
Hostility, units	2.7 ± 3.8	2.6 ± 3.4	.90
Quality of life, units	102 ± 18	105 ± 18	.15

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

*Defined by median weight loss (median = −1.5% in entire overweight/obese group; mean +2% in this subgroup).

Table 4 Impact of Cardiac Rehabilitation and Exercise Training Programs on Coronary Risk Factors in Overweight and Obese Patients without Significant Weight Loss (n = 197)

Characteristics	Before Rehab	After Rehab	% Change	*P* Value
BMI, kg/m^2	29.6 ± 4.0	30.3 ± 4.1	+2%	<.0001
% Fat	30.0 ± 7.2	29.8 ± 7.2	−1%	.95
Total cholesterol, mg/dL	168 ± 35	171 ± 34	+2%	.14
Triglycerides, mg/dL	157 ± 89	147 ± 75	−6%	.08
HDL cholesterol, mg/dL	40.3 ± 11.6	42.7 ± 11.8	+6%	<.0001
LDL cholesterol, mg/dL	98.1 ± 36.1	101 ± 36	+2%	.52
C-reactive protein, mg/dL	4.9 ± 6.2	4.6 ± 7.0	−6%	.28
Fasting glucose, mg/dL	112 ± 32	113 ± 28	+1%	.79
Peak oxygen consumption, mL/kg/min	16.4 ± 4.8	18.2 ± 5.7	+11%	<.0001
Anxiety, units	3.9 ± 4.4	2.1 ± 3.1	−46%	<.0001
Depression, units	3.4 ± 4.0	1.9 ± 2.7	−44%	<.0001
Somatization, units	6.5 ± 4.1	5.0 ± 3.7	−23%	<.0001
Hostility, units	2.7 ± 3.8	2.0 ± 3.1	−26%	<.001
Quality of life, units	102 ± 18	115 ± 16	+13%	<.0001

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

vided by the gold standard percent body fat criteria for obesity, patients with higher baseline percent body fat have considerably lower mortality, confirming that the "obesity paradox" is not a fluke of methodology, and confirming data that we have previously demonstrated in systolic heart failure.[8] Finally, purposeful weight loss in overweight and obese coronary patients does not cause harm, but does lead to marked improvements in coronary risk factors and at least a very slight trend, although not statistically significant, for lower total mortality.

Obesity Paradox

Although epidemiological studies clearly point out the adverse impact that obesity has on overall health, including cardiovascular disease and coronary heart disease,[2,4,6,15] among cohorts of cardiovascular disease patients, obese patients have been noted to have lower major events and mortality during follow-up.[6–15] This "obesity paradox" has been best described in patients with heart failure, particularly systolic heart failure[6-10] but also has been noted with diastolic heart failure.[46] In addition, this obesity paradox recently has been reported in cohorts with hypertension,[6,12,13] and we reported this paradox in large cohorts referred for echocardiography with preserved systolic function,[11] including elderly subjects aged >70 years.[47]

In a major meta-analysis from the Mayo Clinic, Romero-Corral et al[14] analyzed 40 cohort studies totaling over 250,000 patients with coronary heart disease grouped according to BMI. In an analysis of total mortality, the low BMI group had by far the highest mortality, while the obese patients had lower risk. Overweight patients had the lowest relative risk in the adjusted analysis, while obese and se-

Table 5 Impact of Cardiac Rehabilitation and Exercise Training Program on Coronary Risk Factors in Overweight and Obese Patients with Significant Weight Loss (n = 196)

Characteristics	Before Rehab	After Rehab	% Change	*P* Value
BMI, kg/m^2	31.2 ± 4.6	29.7 ± 4.3	−5%	<.0001
% Fat	32.9 ± 8.2	29.8 ± 8.9	−8%	<.0001
Total cholesterol, mg/dL	166 ± 39	162 ± 35	−3%	.070
Triglycerides, mg/dL	155 ± 94	128 ± 71	−17%	<.0001
HDL cholesterol, mg/dL	39.0 ± 11.6	42.8 ± 12.0	+10%	<.0001
LDL cholesterol, mg/dL	98.2 ± 40.3	93 ± 29	−5%	.025
C-reactive protein, mg/dL	6.7 ± 10.3	4.1 ± 5.6	−40%	<.0001
Fasting glucose, mg/dL	113 ± 32	108 ± 26	−4%	.021
Peak oxygen consumption, mL/kg/min	17.1 ± 5.6	19.8 ± 6.9	+16%	<.0001
Anxiety, units	4.1 ± 4.4	2.3 ± 3.2	−43%	<.0001
Depression, units	3.2 ± 3.8	1.7 ± 2.6	−47%	<.0001
Somatization, units	6.6 ± 3.7	4.6 ± 3.7	−31%	<.0001
Hostility, units	2.6 ± 3.4	1.5 ± 2.7	−42%	<.001
Quality of life, units	105 ± 18	118 ± 14	+16%	<.0001

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

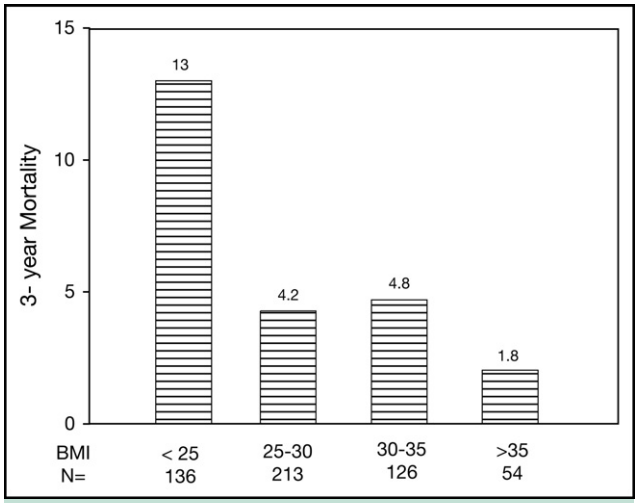

Figure 1 Three-year mortality in 529 coronary patients who attended cardiac rehabilitation grouped by body mass index (BMI). Mortality was inversely related with BMI ($P < .0001$).

verely obese patients had no increased risk. Recently, this paradox also was described in nearly 7000 male non-heart-failure veterans referred for stress testing.[48] Our studies of patients with coronary heart disease confirm the obesity paradox in a group of coronary heart disease patients completing a formal CRET program.

BMI versus Body Fatness

Although BMI is the most common method to define overweightness and obesity in both epidemiological studies and clinical trials, this method does not necessarily reflect true

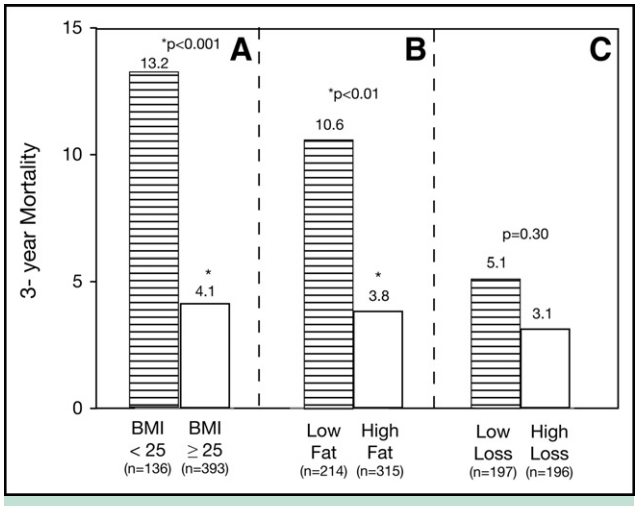

Figure 2 All-cause mortality in 529 coronary patients following formal cardiac rehabilitation: (**A**) divided by baseline body mass index (BMI); (**B**) divided by baseline percent body fat (>25% in men and >35% in women); and (**C**) in 393 patients with baseline BMI ≥25 kg/m^2, divided by median weight change.

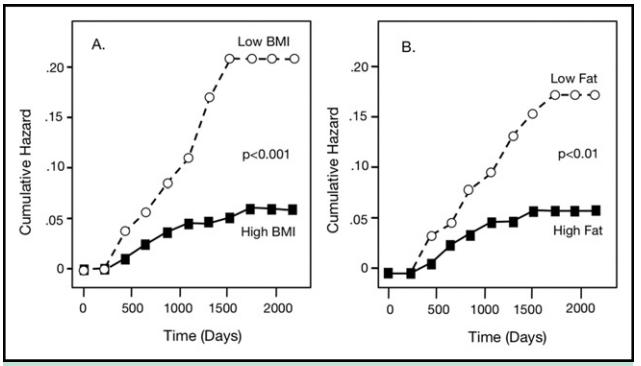

Figure 3 Actuarial cumulative hazard plot for survival time in 529 coronary patients based on: (**A**) Baseline body mass index (BMI) status (high = BMI ≥25 kg/m^2 vs low = BMI <25 kg/m^2) and (**B**) Baseline percent body fat (high = fat >25% in men and >35% in women vs low fat).

body fatness, and BMI/body fatness may differ considerably among various ages, sexes, and races.[6,15-19,49] It has been suggested that a potential explanation for the lack of the expected association between BMI and adverse outcome in patients with coronary heart disease would be the poor diagnostic performance of BMI to discriminate between body fatness and lean body mass, factors that are associated with different and opposing outcomes in cardiovascular disease.[6,14-19,50,51] In fact, the group from the Mayo Clinic recently demonstrated that BMI performed suboptimally to predict obesity as defined by the World Health Organization gold standard (body fat >25% in men and >35% in women).[16,41]

In the present study of patients completing CRET programs after major coronary events, we found that patients classified as overweight/obese by either the standard BMI method or by percent body fat determination had considerably lower mortality during follow-up compared with patients with lower BMI or lower percent body fatness, respectively. In patients with systolic heart failure, we have previously demonstrated that higher percent body fat predicted a lower risk of clinical events[8] and, more recently, a lower all-cause mortality.[52] In the present study of a cohort of coronary patients completing formal CRET, we confirmed the apparent protective effect of higher baseline BMI as well as higher baseline percent body fat on clinical prognosis.

Untangling this puzzling obesity paradox with both BMI and percent body fat is difficult.[6,53] As in most such studies, including ours, the potential role of nonpurposeful weight loss before study entry was not accounted for or specifically measured. However, in general, patients starting phase II CRET programs are quite stable from a noncardiovascular standpoint. Although most studies show a high mortality and cardiac event rate in underweight patients, only 6 of 529 subjects were classified as underweight (BMI <18.5 kg/m^2) in our study. We also did not control for chronic obstructive lung disease, but only a minority of our patients were

actively smoking. Previously our group has reported lower circulating levels of B-type natriuretic peptide associated with obesity, which may cause obese patients to present earlier with less severe disease.[10,54,55] Other lines of evidence have suggested enhanced protection with obesity against endotoxin inflammatory cytokines as well as increased nutritional and metabolic reserve.[10,55] Although this mechanism seems plausible in patients with systolic heart failure, this explanation probably does not explain the obesity paradox in patients with preserved systolic function in the present and other studies.[11,47] Instead, the so-called "obesity paradox" may be partly the result of the inherent potential of adipose tissue to promote or improve metabolic processes, depending upon its pathogenic or physiologic responses to caloric balance. For example, before a cardiovascular event, positive caloric balance leading to adiposity may result in pathogenic adipose tissue responses that cause metabolic disease, many which increase risk.[56-60] Conversely (or paradoxically), during times of negative caloric balance, as may occur during an acute cardiovascular event or major interventional procedures, adipose tissue might conceivably respond with enhanced function that could improve cardiovascular and other clinical outcomes.

Purposeful Weight Loss in Coronary Heart Disease

Observational long-term epidemiological studies have shown that weight loss in overweight and obese people is associated with increased mortality, which would support the notion that overweight and obese may not only have better survival but also may not benefit from purposeful weight reduction.[40] However, studies assessing mortality based on body fat and lean mass rather than BMI or weight alone have shown that subjects losing body fat rather than lean mass have a lower mortality.[40,61] In addition, data have demonstrated that central obesity poses a more significant cardiovascular disease risk than does total obesity and that waist circumference and waist/hip ratio, which were not assessed in our study, may be better predictors of atherosclerosis and cardiovascular disease risk than BMI.[15-19] Nevertheless, it has been suggested that purposeful weight loss may not be beneficial and may even be detrimental in patients with cardiovascular disease.[7,39,40,61]

In the present study, we confirmed the marked improvements in overall coronary risk factors that occur in overweight and obese coronary patients who were more successful with purposeful weight reduction. Previously we have demonstrated the beneficial results of formal CRET in obese patients with coronary heart disease.[4,36-38] In a small subgroup of 45 obese patients with 5% or more (average 10% ± 4%) reduction in body weight following CRET, we noted significant improvements in exercise capacity, total cholesterol, HDL cholesterol, LDL cholesterol, and LDL/HDL ratio, with much less improvement in 81 obese patients who did not lose weight.[37] In a much larger sample size in the present study, we demonstrated the impact of CRET on these factors as well as on improving inflammation (CRP) and fasting glucose in obese patients who were more successful with weight reduction. The marked improvement in CRP levels associated with weight reduction may be clinically important because levels of CRP and leptin, an adipocyte hormone involved in CRP synthesis, have predicted cardiovascular events in obesity.[62] Moreover, weight loss in coronary patients was not associated with a worse short-term prognosis, and instead, there was a slight trend for lower mortality in overweight and obese coronary patients who lost more weight. These results are consistent with the idea that weight loss associated with fat loss while maintaining (as noted in our patients) or improving lean mass content appeared to be beneficial. Likewise, in a study of over 1500 coronary heart disease patients, intentional weight loss from a 6-month dietary program also produced a lower incidence of coronary events over 4 years.[63] Finally, a recent study of 377 consecutive coronary patients from the Mayo Clinic described better event-free survival associated with weight loss, including marked benefits in those with BMI <25 kg/m^2 and ≥ 25 kg/m^2.[64] Taken together, these studies support purposeful weight reduction in overweight and obese coronary heart disease patients, despite the "obesity paradox."

Study Limitations

Certainly, selection bias could contribute to our study findings, in that the patients we studied chose to attend and complete CRET, and we retrospectively assessed patients who were more successful with weight loss compared with those who were less successful. It should be emphasized that our study number was relatively small, particularly in the low BMI cohort, and our average follow-up for total mortality was just over 3 years. In addition, although we assessed the obesity paradox by using percent body fat assessment in addition to BMI, our method to assess body fat (sum of the skin-fold method), although validated, is not considered to be as accurate as some other methods (eg, hydrostatic weighing, air displacement plethysmography, bioelectrical impedance, x-ray absorptiometry).[15,16,44,65] We also did not assess other surrogate markers of "at risk" obesity, such as waist circumference or waist/hip ratio, which have been shown to predict atherosclerosis burden and clinical events.[15-19] Also, we assessed the effects of CRET on standard risk factors and all-cause mortality, but our follow-up data do not allow us to accurately assess cardiovascular events, cardiovascular mortality, or noncardiovascular morbidity/mortality. Finally, our results do not provide data about the mechanisms of these effects, nor do they explain the discrepancy of why higher weight and higher percent body fat may be detrimental in primary prevention but protective in patients with cardiovascular disease, and why purposeful reduction of both weight and percent fat appear to be safe and efficacious. Therefore, we cannot conclude that this obesity paradox is casual rather than merely an association noted in cohorts with cardiovascular disease. Finally, although this "obesity paradox" has now been con-

firmed in numerous trials that have been recently reviewed in detail,[6] it must be acknowledged that a randomized, prospective trial of a greater number of patients over a much longer time period could reveal different results.

CONCLUSIONS

Although an obesity paradox exists, in that coronary heart disease patients with higher BMI or higher percent body fat have lower mortality than those with less obesity, these results support the safety and potential long-term benefits of purposeful weight loss in overweight and obese patients with coronary heart disease.

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