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Clinical Investigations

Severity of Coronary Artery Disease in Obese Patients Undergoing Coronary Angiography: "Obesity Paradox" Revisited

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Summary

Background: Recent studies have highlighted the existence of an 'obesity paradox' in patients undergoing coronary angiography, i.e., a high body mass Index (BMI) is associated with less severe coronary lesions. We sought to confirm the existence of this phenomenon in the US patient population.

Methods: Study subjects included 770 consecutive patients (470 men, 428 African-Americans, 212 Caucasians) referred for coronary angiography to a tertiary care center. Duke myocardial jeopardy score, a prognostication tool predictive of 1-year mortality in coronary artery disease (CAD) patients, was assigned to angiographic data. Patients were classified according to their BMI (kg/m^2) as normal (21–24), overweight (25–29), obesity class I (30–34), class II (35–39) and class III (40 or above).

Results: Patients in the increasing obesity class had a higher prevalence of diabetes, hypertension and dyslipidemia and were more likely to be women. A negative correlation was observed between BMI and age ($R = -0.15$ $p < 0.001$) as well as between BMI and Duke Jeopardy score ($r = -0.07$, $p < 0.05$) indicating that patients with higher BMI were referred for coronary angiography at a younger age, and had a lower coronary artery disease (CAD) burden. BMI was not an independent predictor of coronary lesion severity on multivariate stepwise linear regression analysis.

Conclusion: Obese patients are referred for coronary angiography at an earlier age and have a lower CAD burden lending further credence to the existence of an apparent "obesity paradox". However, obesity per se, after adjustment for comorbidities, is not an independent predictor of severity of coronary artery disease.

Key words: obesity, body mass index, coronary artery disease, duke myocardial jeopardy score, reverse epidemiology

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Introduction

The prevalence of obesity in westernized society is trending upward and has achieved epidemic proportions in the US population.[1,2] There is a growing recognition that obesity adversely influences traditional cardiovascular risk factors such as hypertension, plasma lipids, diabetes mellitus and the metabolic syndrome and therefore the American Heart Association (AHA) defines obesity as a strong risk factor for coronary artery disease (CAD).[3] Although obesity has been implicated as an independent risk factor for CAD events in the general population, recent evidence has alluded to the presence of

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an apparent paradoxical relationship between obesity and cardiovascular prognosis in certain subsets of patients. In particular, data indicate that short-term outcomes and survival in patients with heart failure[4,5] and in patients following coronary revascularization[6–12] appear to be paradoxically better in obese compared to lean patients (obesity paradox). Indeed, the "obesity paradox" theme has generated considerable debate in recent literature;[13] a study from Israel examined the relation between body mass index (BMI) and extent of CAD and suggested that obesity be considered a 'negative predictor' of coronary artery disease severity in patients referred for coronary angiography.[14] We attempted to explore this hypothesis in the US population.

Methods

Study Population

The study group consisted of 770 consecutive patients, who underwent coronary angiography, for acute coronary syndrome or stress test positivity from January 2005 to October 2005 at a tertiary care center. Patient demographics and medical history including cardiovascular risk factor profile (age in years, gender, diabetes mellitus as per American Diabetic Association criteria, dyslipidemia per National Cholesterol Education Program screening criteria, hypertension per Joint National Committee 7 criteria, cigarette smoking and family history of coronary artery disease) were abstracted from patient charts. As required by the hospital policy, the Institutional Review Board of the University reviewed and approved the protocol in compliance with Health Insurance Portability and Accountability Act (HIPAA) for investigator's participation in the study prior to data utilization.

Obesity was classified according to the BMI using the National Institutes of Health (NIH) criteria as Normal (BMI 21–24 kg/m^2), overweight (BMI 25–29 kg/m^2), obesity class I (BMI 30–34 kg/m^2), Obesity class II (BMI 35 to 39 kg/m^2 and obesity class III (BMI 40 or above kg/m^2). Coronary angiography data were obtained from the Siemens Queries software system, which maintains the database including detailed angiographic findings of all patients at this institution.

Significant lesions were defined as those with >70% diameter narrowing of coronary arteries (>50% for the left main coronary artery). We attempted to quantify the "severity of CAD" by ascertaining the prevalence of high-risk coronary anatomy (HRCA, defined as >50% stenosis of the left main coronary artery and/or significant three-vessel coronary artery disease) and "CAD burden" by computing myocardial jeopardy scores from anatomic representation of the myocardium-at risk, based on the size and distribution of coronary lesions. In accordance with the Duke Jeopardy Scoring system, the coronary tree was divided into six segments: the left anterior descending (LAD) coronary artery, diagonal branches of LAD, septal perforating branches, the circumflex coronary artery, obtuse marginal branches, and posterior descending coronary artery (PDA). Each segment of myocardium distal to 70% stenosis was considered to be at risk and was assigned a score of two. A score from 0–12 was designated to each coronary angiogram depending on the number of segments involved.[15] Patients with a history of bypass grafting surgery were excluded from the study due to the inability to estimate Duke myocardial jeopardy scores in this subset of patients

Statistical Analysis

Statistical analyses were performed using the SPSS 13.0 software package

(SPSS, Inc., Chicago, Illinois). Continuous (Scale) data are presented as Mean ± Standard Error (SE). Differences in group means were assessed using independent Student's t test and likelihood ratio chi-square test, as appropriate.

Pearson correlation analysis (r = correlation coefficient) was utilized to determine unadjusted bivariate correlation between two variables (BMI, Age and Duke

Score were scale variables in this study). We conducted multivariate analysis using stepwise multiple linear regressions to examine the relation of Duke Myocardial Jeopardy Score and BMI adjusting for other cardiovascular risk factors. A 2-tailed p value of < 0.05 was considered statistically significant for all analysis.

Results

Our study cohort comprised of 770 consecutive subjects including 428 African–Americans and 212 Caucasians; 300 (39%) women and 470 (61%) men (mean age of 60.6 (Median 60, range 25 to 91) years and mean BMI of 30.1 (Median 29.2, range 19 to 55) kg/m^2. Patients belonging to higher obesity classes were significantly younger at the time of coronary angiography and a trend toward lower mean age was observed through each increasing obesity class (Fig. 1). Higher obesity classes were associated with a higher prevalence of diabetes mellitus (chi-square 30.1, $p < 0.001$), hypertension (chi-square 12.3, $p < 0.05$) and dyslipidemia (chi square 17.0, $p = 0.002$) (Table 1). A nonsignificant trend toward lower prevalence of smoking and a higher prevalence of family history of coronary artery disease was noted among higher obesity classes. Although a trend toward lower prevalence of left main disease and HRCA was apparent with increasing obesity class, the difference did not reach statistical significance (Table 2). No statistically significant association was observed between obesity class and

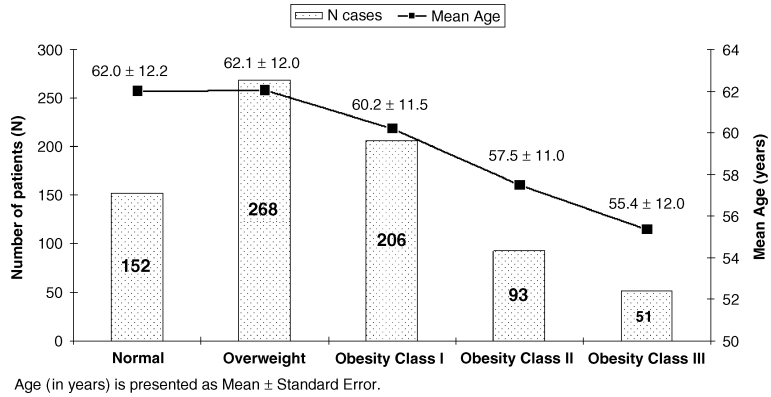

FIG. 1 Obesity classification and age at the time of coronary angiography.

TABLE 1 Baseline Characteristics of study subjects in relation to obesity class

	Normal	Overweight	Obesity class I	Obesity class II	Obesity class III	p value
Men	110 (72.4%)	177 (66.0%)	126 (61.2%)	46 (49.5%)	11 (21.6%)	<0.001*
Race						0.12
Caucasians	42 (28.2%)	77 (29.6%)	61 (30.5%)	20 (22.0%)	12 (25.0%)	
African–Americans	86 (57.7%)	134 (51.5%)	114 (57.0%)	63 (69.2%)	31 (64.6%)	
Others	21 (14.1%)	49 (18.8%)	25 (12.5%)	8 (8.8%)	5 (10.4%)	
Diabetes mellitus	34 (22.4%)	86 (32.1%)	69 (33.5%)	49 (52.7%)	26 (51.0%)	<0.001*
Hypertension	99 (65.1%)	189 (70.5%)	132 (64.1%)	75 (80.6%)	40 (78.4%)	0.02*
Dyslipidemia	89 (58.6%)	164 (61.2%)	117 (56.8%)	73 (78.5%)	26 (51.0%)	0.002*
Smoking	72 (47.4%)	102 (38.1%)	68 (33.0%)	32 (34.4%)	17 (33.3%)	0.07
Family H/o CAD	32 (21.1%)	63 (23.5%)	49 (23.8%)	28 (30.1%)	18 (35.3%)	0.23

CAD = Coronary Artery Disease.

prevalence of either normal angiogram, one, two or three-vessel disease. However, comparing overall obese (BMI $\geq$ 30) vs. nonobese groups, a statistically significant low prevalence of HRCA was encountered in the obese group (97 of 420, 23.1% vs. 62 of 350, 17.7%, $p < 0.05$); in the group with severe obesity (BMI $\geq$ 35 kg/m^2) alone, left main disease was encountered less frequently (47 of 626, 7.5% vs. 3 of 144, 2.1%; $p < 0.05$).

Upon further review of angiograms and after assigning Duke Jeopardy scores, a trend toward lower CAD burden was noticed among higher obesity classes by chi

TABLE 2 Angiographic findings in relation to obesity class

	Normal	Overweight	Obesity class I	Obesity class II	Obesity class III	p value
Normal angiogram	12 (7.9%)	16 (6.0%)	13 (6.3%)	5 (5.4%)	4 (7.8%)	0.92
One vessel CAD	66 (43.4%)	127 (47.4%)	95 (46.1%)	39 (41.9%)	25 (49.0%)	0.84
Two Vessel CAD	43 (28.3%)	59 (22.0%)	59 (28.6%)	33 (35.5%)	15 (29.4%)	0.12
Three-vessel CAD	22 (15.4%)	44 (17.9%)	23 (12.1%)	14 (15.4%)	6 (12.0%)	0.52
Left main stenosis	9 (5.9%)	22 (8.2%)	16 (7.8%)	2 (2.2%)	1 (2.0%)	0.09
HRCA	31 (20.4%)	66 (24.6%)	39 (18.9%)	16 (17.2%)	7 (13.7%)	0.27
Duke jeopardy score						0.02*
0	12 (7.9%)	16 (6.0%)	13 (6.3%)	5 (5.4%)	4 (7.8%)	
2	50 (32.9%)	116 (43.3%)	83 (40.3%)	36 (38.7%)	22 (43.1%)	
4	54 (35.5%)	57 (21.3%)	63 (30.6%)	31 (33.3%)	13 (25.5%)	
6	15 (9.9%)	39 (14.6%)	24 (11.7%)	12 (12.9%)	11 (21.6%)	
8	10 (6.6%)	14 (5.2%)	6 (2.9%)	7 (7.5%)	0 (0.0%)	
10	3 (2.0%)	12 (4.5%)	3 (1.5%)	1 (1.1%)	0 (0.0%)	
12	8 (5.3%)	14 (5.2%)	14 (6.8%)	1 (1.1%)	1 (2.0%)	

CAD = coronary artery disease; HRCA = high-risk coronary anatomy.

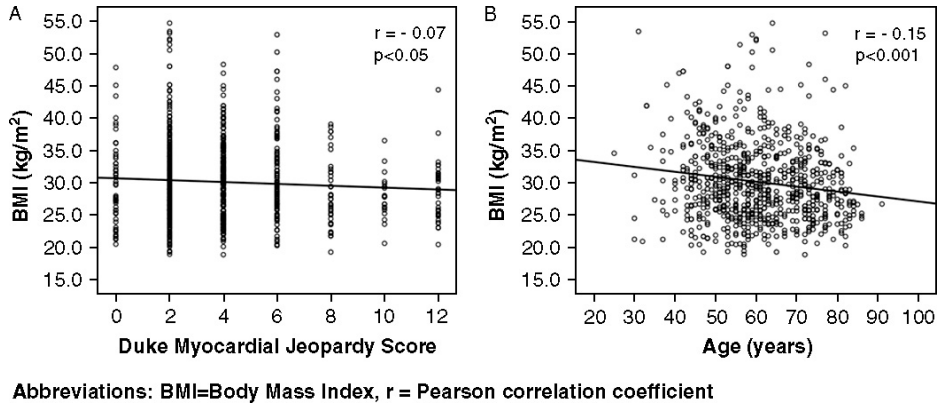

FIG. 2 Correlation between body mass index (BMI) and Duke myocardial jeopardy score (A) or age during coronary angiogram (B).

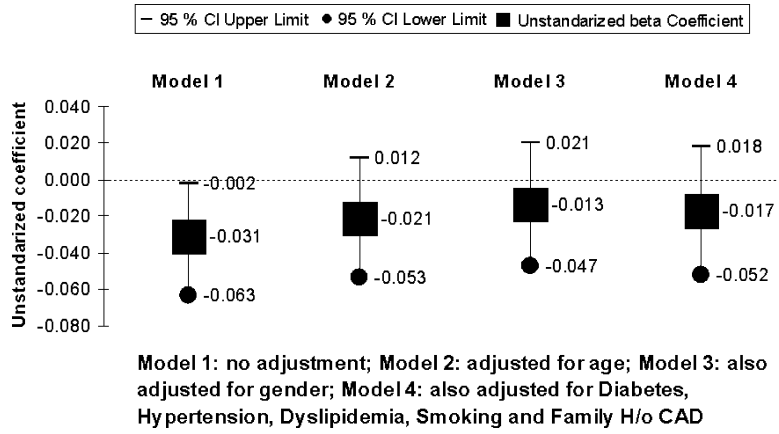

FIG. 3 Correlation coefficients from linear regression models relating Duke jeopardy score as a continuous variable to body mass index (BMI).

square analysis (Table 2). This inverse relationship was also confirmed on bivariate Pearson correlation analysis between BMI and Duke Score ($r = -0.07$, $p < 0.05$, Fig. 2(A)). Notably, BMI correlated negatively with patient age at the time of coronary angiography ($r = -0.15$, $p < 0.001$) (Fig. 2(B))

To determine the effect of obesity as an independent predictor of coronary lesion severity, multivariate analysis was performed with stepwise multiple linear regression models using Duke Jeopardy Score as a dependent scale variable and BMI as an independent variable while adjusting for age, gender, diabetes, hypertension, dyslipidemia, smoking and family history of CAD. Multivariate analysis revealed a significant crude association between Duke Score and BMI in the unadjusted model (unstandardized coefficient $\pm$ Standard Error $= -0.031 \pm 0.016$; $p < 0.05$) that was attenuated to nonsignificance after adjustment for age and other cardiovascular risk factor (unstandardized coefficient $\pm$ Standard Error $= -0.017 \pm 0.018$; $p = 0.34$, Fig. 3)

A positive correlation was observed between age and Duke score on bivariate Pearson correlational analysis ($r = 0.15$, $p < 0.001$) suggesting that the apparent negative association observed between Duke scores and BMI was likely influenced by the fact that obese patients were being referred for coronary angiography at an earlier age.

Discussion

Our findings suggest that obese patients being referred for coronary angiography have a paradoxically lower CAD burden (Duke myocardial jeopardy scores) and prevalence of high-risk coronary anatomy (significant left main or triple vessel disease) compared to their nonobese comparators despite a higher prevalence of diabetes, hypertension and dyslipidemia, implying the presence of an apparent "obesity paradox". However, after adjusting for other major cardiovascular risk factors, BMI was no longer an independent predictor of CAD burden or severity on multivariate stepwise linear regression analysis. We also observed a negative association between BMI and age indicating that patients with

a higher BMI were being referred for coronary angiography at a younger age.

The "obesity epidemic" has affected nearly 70% of the current adult US population in comparison to less than 25% about 40 years ago.[1,2] Obesity has traditionally been considered a cardiovascular risk factor and has been associated with an increased risk of developing CAD and mortality in the general population. Thus, it may be speculated that obese patients should have worse outcomes than their nonobese counterparts; however, recent publications have suggested that obesity may actually be associated with better outcomes in patients with CAD undergoing revascularization procedures.[6–12] This paradoxical observation relating obesity to better clinical outcome is known as the "obesity paradox" and has also been reported in other cardiovascular diseases including acute coronary syndromes[16,17] and heart failure.[4,5]

The phenomenon of an established risk factor in the general population having a markedly different predictive pattern is not unique to cardiovascular diseases but has also been observed in patients with end-stage renal disease (ESRD) undergoing dialysis,[18] elderly individuals in nursing homes[19] and hospitalized patients.[20]

A recent study from Israel by Rubinshtein *et al.*[14] showed that obesity was associated with less severe coronary artery disease among patients undergoing coronary angiography. Obese patients were found to have a low prevalence of HRCA (23 % vs. 37% compared to nonobese comparators, $p = 0.002$). Further, obese patients were referred for coronary angiography at an earlier age than their nonobese counterparts. In our study, patients in higher obesity classes were more likely to be women and had a higher prevalence of diabetes mellitus, systemic hypertension and dyslipidemia. Similar to the previous report, we found HRCA to be less prevalent among patients with BMI >30; in particular, left main disease was less frequent in patients with BMI >35. We applied the Duke myocardial jeopardy scoring system, a validated prognostication tool (also an index of CAD burden) predictive of 1-year mortality in patients treated medically or with percutaneous intervention to statisfy our study cohort.[15] A paradoxical negative association was evident between BMI and CAD burden in the bivariate correlational analysis, ostensibly, lending further credibility to this hypothesis. While these findings may be supportive of an apparent "obesity paradox," we would advocate caution against a simplistic interpretation of this relation; specifically, the need to discriminate a "risk association" from a "causal association" in this scenario has to be recognized. In our study, upon adjusting for cardiovascular traditional major risk factors including age, gender, diabetes, hypertension and hypercholesterolemia, BMI was no longer a predictor of CAD burden as assessed by the Duke myocardial jeopardy score. We noted a trend toward lower mean age for the patients at the time of referral (for angiography), consistently among each obesity class. Although obese patients were found to have a lower CAD burden and lesion severity, these findings appear to be mitigated by the fact that obese patients were referred for coronary angiography at an earlier age. Our observations, although speculative, seem to also implicate the "tendency or bias of physicians" to refer obese patients (particularly those with additional cardiovascular risk factors) for angiography more liberally; the lower threshold for the decision to define coronary anatomy presumably driven by a higher prevalence of pronounced symptomatology, disability, and comorbidities frequent in overweight patients.

Limitations

Although other potentially confounding variables like physical inactivity, socioeconomic factors, etc may have influenced our results, these were not studied, as this data was not readily available. We however analyzed the influence of the more widely recognized traditional cardiovascular risk factors, defined in prior studies.[21] The apparent negative association between obesity and CAD severity found in our study population appears to be mostly a reflection of physician practice patterns, in particular, the fact that obese patients were referred for coronary angiography at a younger age. Being a cohort study from a single institution, cohort selection bias cannot be excluded. Finally, while our conclusions cannot be extrapolated to the general population, they appear to be hypothesis generating and deserve future exploration in a larger multicenter study.

Conclusion

In summary, obesity is negatively associated with coronary artery disease burden (Duke myocardial jeopardy score) and severity (HRCA and left main disease) at the time of coronary angiography suggesting the existence of an apparent "obesity paradox" in the US population. However, BMI per se should not be considered a "negative predictor" of CAD burden. It appears that obese patients are more likely to be referred for coronary angiography at a younger age. While the underlying mechanisms of the obesity paradox remain somewhat obscure, age appears to play a confounding role and awareness of this relationship is relevant to the clinical management and risk assessment of obese patients with cardiac symptoms, in particular when coronary angiography is contemplated.

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