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Clinical Investigations

Obesity Is Associated with Premature Occurrence of Acute Myocardial Infarction

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Summary

Background: The American Heart Association has classified obesity as a major modifiable risk factor for coronary artery disease, but its relationship with age at presentation with acute myocardial infarction (AMI) is poorly documented.

Hypothesis: The study was undertaken to evaluate the impact of obesity on age at presentation, and on in-hospital morbidity and mortality in patients with AMI.

Methods: Our analysis includes a consecutive series of 906 Olmsted County patients (mean age 67.7 years, 51% male) admitted with AMI to the Mayo Clinic Coronary Care Unit (CCU). The patients were entered into the Mayo CCU Database, a prospective registry of data pertaining to patients admitted to the Mayo Clinic CCU with AMI. Age at AMI occurrence and in-hospital morbidity and mortality were noted.

Results: Obese patients (body mass index [BMI] >30) with AMI were significantly younger than patients with AMI in the overweight (BMI 25–30) and normal-weight (BMI <30) groups (62.3 ± 13.1 vs. 66.9 ± 13.2 and 72.9 ± 13.4, respectively, $p<0.001$). Obesity and overweight status were associated with male gender, diabetes mellitus, hypercholesterolemia, and smoking history; however, after multivariate adjustment for these risk factors, excess weight and premature AMI remained significantly associated. Compared with normal-weight patients, overweight patients presenting with AMI were 3.6 years younger ($p<0.001$, confidence interval [CI] 1.9–5.4) and obese patients 8.2 years younger ($p<0.001$, CI 6.2–10.1). No significant increase in in-hospital morbidity and mortality was seen.

Conclusion: In this population-based study, overweight and obese status are independently associated with the premature occurrence of AMI, but not with an increased incidence of in-hospital complications.

Key words: obesity, acute myocardial infarction, mortality, coronary artery disease, age

Introduction

The role of obesity as an independent risk factor for coronary atherosclerosis is controversial. The relationship between obesity and coronary atherosclerosis was formerly thought to be indirect, since obesity often coexists with other cardiovascular risk factors, including hyperlipidemia, hypertension, and diabetes;[1–3] several subsequent long-term longitudinal studies, however, have demonstrated that obesity is an independent risk factor for coronary atherosclerosis,[4–11] and the American Heart Association (AHA) has recently classified obesity as a major, modifiable risk factor for coronary heart disease.[12, 13] To date, the impact of obesity on age of first presentation with AMI and on subsequent in-hospital complications and mortality has been poorly defined. Analysis from the Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico (GISSI-2) trial has suggested that increasing body mass index (BMI) is associated with a greater relative risk of AMI in individuals aged <55 years compared with those ≥ 55 years.[8] Despite the GISSI-2 data suggesting a link between obesity and premature presentation with AMI, no study to date has examined the effect of obesity on age at presentation and outcome in AMI patients. Our investigation examines the relationship between obesity and age at presentation with AMI, AMI treatment strategies in a defined geographic population, and in-hospital mortality resulting from AMI. Effects of referral bias were minimized by studying a defined geographical population, that is, residents of Olmsted County, Minn.

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Methods

Purpose of the Database

The Mayo Clinic Coronary Care Unit (CCU) database, used for this study, prospectively collects data on all patients admitted with AMI to the Mayo CCU at Saint Marys Hospital. This report includes only patients who were residents of Olmsted County at the time they had an AMI, and who gave informed consent as required by Minnesota Statute 144.335. The investigation was approved by the Mayo Institutional Review Board prior to data analysis. Data were collected from the clinical record by a single data-collection specialist according to predefined criteria for each datapoint after a patient's hospital discharge. This work was monitored by the physician CCU Database Coordinator with adjudication of events by the CCU Database Steering Committee when indicated.

Definitions

Acute myocardial infarction was defined for this study according to World Health Organization criteria,[14] based on symptoms, electrocardiographic (ECG) findings, and cardiac enzyme abnormalities. Symptom onset was defined as the time at which chest pain grew intense, prolonged, or intolerable enough to lead the patient to seek treatment. Time of initial presentation was defined as the time of the patient's arrival at the hospital. Acute myocardial infarction was classified as ST-segment elevation (STE) or non-STE, based upon the presence or absence of > 1 mm of STE in two or more contiguous leads on the initial ECG. Primary reperfusion therapy was defined as use of intravenous fibrinolytic therapy, percutaneous transluminal coronary angioplasty (PTCA), or immediate coronary artery bypass graft (CABG) surgery as the initial therapy to restore blood flow through a coronary artery suspected or known to be occluded. Use of adjunct therapy during hospitalization was recorded for every patient. Killip classification was used to risk-stratify patients upon admission to the hospital, according to the original definitions by Killip and Kimball.[15]

Obesity was defined on the basis of BMI: weight in kilograms divided by height in meters squared (kg/m^2). Since 1998, the AHA has defined "obesity" as a BMI > 30 kg/m^2, "overweight" as a BMI between 25 and 30 kg/m^2, and "normal" as a BMI < 25 kg/m^2.[13] The presence of diabetes mellitus was determined by the documentation in the patient's previous or current medical record of a documented diagnosis of diabetes mellitus that had been treated with medication or insulin. Information was obtained in all diabetics from the medical record with regard to previous documentation of any of the following sequelae of diabetes mellitus: renal disease, retinopathy, peripheral neuropathy, gastroparesis, or peripheral circulatory disease. Information was not collected on the case report form with regard to fasting glucose levels or hemoglobin A_1C values. Previous investigators have demonstrated that screening for the prevalence of diabetes can be satisfactorily performed by this method.[16] The presence of hyperlipidemia was determined by the demonstration of a fasting cholesterol > 200 mg/dl in the patient's medical record, or any history of treatment for hyperlipidemia by the patient's physician. The presence of hypertension was determined by any documentation in the medical record of hypertension or by the patient on treatment for hypertension.

Complications were defined according to their occurrence in any of four categories. Electrical complications included supraventricular tachycardia, ventricular tachycardia or fibrillation, cardiac arrest, electromechanical dissociation, and any arrhythmia resulting in hemodynamic compromise or requiring D/C shock treatment or medical therapy. Ischemic complications included recurrent myocardial infarction, cardiogenic shock, and congestive heart failure. Mechanical complications were defined as cardiac tamponade, acute ventricular septum defect, papillary muscle rupture, and free-wall rupture. Bleeding complications included ischemic or hemorrhagic stroke, gastrointestinal bleed/genitourinary bleed, and hematoma (retroperitoneal or vascular access). Cause of death was determined by autopsy when authorized, or by review of the patient's chart when autopsy was not an option.

Statistical Analysis

Procedures used to identify variables that exhibit statistically significant trends toward increase or decrease across the three ordered weight categories (normal, overweight, and obese) included the Mantel-Haenszel test for the bivariate and ordered categorical variables, and the general linear F test for continuous variables. Pearson's chi-square test was used in testing nonordinal categorical variables for equal distributions, but not for linear trend. Multiple linear regression (using indicator variables), logistic regression, and proportional-hazards models produced adjusted comparisons of clinical outcomes among the three weight groups. The adjustment models were built around prior knowledge of the key predictors in this population by means of a forward, stepwise procedure. All characteristics and treatment variables were included in the initial model, and those that appeared to be influencing outcome or any other desired measure ($p < 0.1$) were included in the final model analysis. The Bonferroni inequality was used to aid in the interpretation of fitted model results from which joint confidence intervals were constructed. Statistical significance implies a p value of ≤ 0.05, and all statistical tests were two-sided. The ethnic mix of our population was approximately 98% Caucasian, 1% Asian, 0.5 % Hispanic and 0.5% African-American.

Results

Patient Characteristics

The study population comprised a consecutive series of 906 Olmsted County resident patients admitted to Saint Marys Hospital with AMI from January 1, 1988, to March 31, 1998. Of these patients, 306 were of normal weight (Group 1),

TABLE I Baseline clinical characteristics

Demographics	BMI < 25 Group 1 (n = 306)	BMI 25–30 Group 2 (n = 362)	BMI > 30 Group 3 (n = 238)	p Value
Male (%)	149 (48.7)	150 (69.1)	159 (66.8)	<0.001
Female (%)	157 (51.3)	112 (30.9)	79 (33.2)	<0.001
Age in years (mean ± SD)	72.9 ± 13.4	66.9 ± 13.2	62.3 ± 13.1	0.001
Diabetes (%)	27 (8.8)	56 (15.5)	63 (26.5)	0.001
Smoking history (current or previous) (%)	166 (54.2)	234 (64.6)	156 (65.5)	0.005
Hypercholesterolemia (%)	136 (44.4)	168 (46.4)	128 (53.8)	0.035
Hypertension (%)	141 (46.1)	149 (41.2)	112 (47.1)	0.9
Family history of CAD (%)	51 (16.7)	63 (17.4)	47 (19.8)	0.36
Prior AMI (%)	67 (21.9)	84 (23.2)	44 (18.5)	0.38

Abbreviations: BMI = body mass index, SD = standard deviation, CAD = coronary artery disease, AMI = acute myocardial infarction.

362 were overweight (Group 2), and 238 were obese (Group 3). Mean body indices were 22.3 ± 2.1 kg/m^2 for Group I; 27.2 ± 1.4 kg/m^2 for Group 2; and 34.5 ± 5.5 kg/m^2 for Group 3. Overweight and obese patients differed significantly from those who were not overweight with respect to multiple baseline clinical variables, as demonstrated in Table I. These patients were more often male, had concomitant diabetes mellitus and hyperlipidemia, and were more likely to be current or former tobacco users. Overweight and obese patients were also significantly younger than were normal-weight patients at presentation with AMI. We compared our study population against an age-matched and geographically matched control group, and found the study group to have a higher average BMI.

Impact of Obesity on Age of Presentation with Acute Myocardial Infarction

We noted a highly significant correlation between BMI and age at presentation with AMI. Figure 1 depicts the adjusted and unadjusted relationship of obesity to patient age at presentation. Obese patients are likely to have onset of AMI at 8.2 years younger than normal-weight patients after adjustment for gender, smoking status, prodromal angina, Killip class, history of prior AMI, diabetes mellitus, and hyperlipidemia. The overweight classification was associated with early onset of AMI by a median postadjustment value of 3.6 years. The observations of premature AMI onset in obese patients ($p < 0.001$) and overweight patients ($p < 0.001$) were highly significant and independent of other variables after multivariate adjustment.

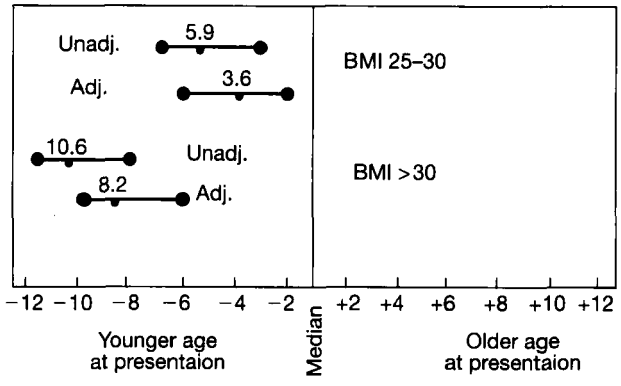

FIG. 1 The influence of body mass index (BMI) on age of presentation for acute myocardial infarction. Adjusted refers to multivariate adjustments; unadjusted refers to raw data.

Myocardial Infarction Characteristics

Obese patients were most likely to present with nonanterior AMI; slightly more than half of patients in all groups presented with ST-elevation AMI, as shown in Table II. No significant differences were seen between groups in the time interval between symptom onset and hospital admission, or with regard to Killip classification at the time of AMI presentation.

Treatment Strategies

Treatment strategies for AMI are presented in Table III. A significantly greater proportion of obese patients were treated with primary reperfusion therapy than were patients in the other weight groups, resulting principally from the proportion of patients who underwent primary PTCA. Overweight and obese patients were also more likely than normal-weight patients to be treated with aspirin and beta-adrenergic blocking agents. No significant differences were seen, however, with regard to treatment with nitrates, heparin, or angiotensin-converting enzyme inhibitors.

In-Hospital Mortality and Left Ventricular Function

Overall in-hospital mortality was comparable among obese, overweight, and normal-weight individuals, but a trend

TABLE II Myocardial infarction profiles of the study groups

	Group 1 (n = 306)	Group 2 (n = 362)	Group 3 (n = 238)	p Value
ST-elevation AMI (%)	161 (52.6)	190 (52.5)	127 (53.4)	0.87
Anterior AMI (%)	132 (43.1)	131 (36.2)	78 (32.8)	0.012
Symptom onset to admission (hours) (mean ± SD)	4.9 ± 7.7	4.6 ± 8.7	4.0 ± 5.8	0.26
Killip class >1 (%)	72 (23.6)	68 (18.8)	54 (22.7)	0.70

Abbreviations as in Table I.

TABLE III Acute myocardial infarction—treatment strategies

	Group 1 (n = 306)	Group 2 (n = 362)	Group 3 (n = 238)	p Value
Primary PTCA (%)	53 (17.3)	82 (22.6)	74 (31.1)	< 0.001
Thrombolytics (%)	61 (19.9)	82 (22.6)	74 (31.1)	NS
Primary reperfusion (total) (%)	115 (37.6)	168 (46.4)	135 (56.7)	< 0.001
Adjunctive therapy within 24 h of admission				
Aspirin (%)	223 (72.9)	296 (81.8)	198 (83.2)	0.002
Beta blocker (%)	182 (59.5)	253 (69.9)	165 (69.3)	0.011
Nitrates (%)	249 (81.4)	320 (88.4)	201 (84.4)	0.238
ACEI (%)	37 (12.1)	38 (10.5)	34 (14.3)	0.377
Heparin (%)	274 (89.5)	336 (92.8)	219 (92.0)	0.265

Abbreviations: PTCA = percutaneous transluminal coronary angioplasty, NS = not significant, ACEI = angiotensin-converting enzyme inhibitor.

TABLE IV In-hospital outcome

	Group 1 (n = 306)	Group 2 (n = 362)	Group 3 (n = 238)	p Value
Death (%)	36(11.8)	31 (8.6)	21 (8.8)	0.22
Nonfatal complications (%)	71 (23.2)	78 (21.6)	37 (15.6)	0.03
EF (mean ± SD)	47.6 ± 16.4	49.2 ± 15.7	50.9 ± 14.0	0.04

Abbreviations: EF = left ventricular ejection fraction measured closest to the time of discharge, SD = standard deviation.

toward reduced mortality in the obese and overweight patients was seen, as shown in Table IV. After controlling for age, gender, Killip class, primary reperfusion, aspirin and beta-blocker therapy, the adjusted in-hospital mortality between study groups remained comparable. Fewer nonfatal in-hospital complications were seen in obese patients than in other patients studied. After adjustment for age, gender, diabetes mellitus, smoking history, AMI location, and primary reperfusion therapy, these differences were significant only for obese patients: Group 3 versus Group 1 (odds ratio [OR] 0.53, 90% confidence interval [CI]: 0.33, 0.84, p = 0.018). Figure 2 illustrates our between-groups observations of BMI in-hospital mortality and in-hospital complications. Evaluation of patients' left ventricular function at the time of discharge revealed a trend toward better left ventricular ejection fraction in obese patients than in patients in the other two groups.

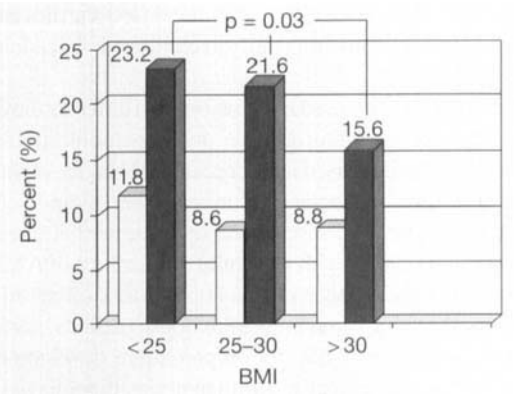

FIG. 2 The influence of unadjusted body mass index (BMI) on in-hospital mortality and acute myocardial infarction complication rates. □ = In-hospital mortality, ■ = in-hospital complications.

Discussion

In this first prospective study to evaluate the relationship between obesity and age at presentation with AMI in a geographically defined population, we found that obesity is independently associated with premature occurrence of AMI. Our observation is consistent with the recent recognition that obesity is a major risk factor for coronary artery disease (CAD) development.[12, 13] Our hypothesis that increased body mass is an important marker for the premature presentation of AMI is supported by a comparison between our study population and an age-matched control group; patients in our study group, on average, had higher BMIs. Even after adjustment for confounding variables, obese patients were likely to present with AMI nearly a decade younger than normal-weight patients. Our observations agree with those of an earlier report that suggests a causal relationship between obesity and premature risk for AMI,[9] and are consistent with previous work showing a significant association between obesity and other cardiovascular risk factors, including diabetes, hypertension, and hypercholesterolemia.[17]

Obesity is increasing in prevalence worldwide. The Third National Health and Nutrition Examination Survey (NHANES III) (1988–1991) estimates that 33% of the U.S. population is obese, a significant increase over the 25% estimate reported in NHANES II (1976–1980).[18] This parallels reports of increased prevalence of obesity in Europe over the past decade: 10 versus 40%.[19] Epidemiologists have observed both an emerging epidemic of cardiovascular disease in many developing countries, and an accompanying prevalence of increased body weight.[20] In the United States, where the high prevalence of obesity is evident in both children and adults, more than 20% of children aged 6 to 17 years are overweight.[21, 22] Some investigators contend that more than half of overweight children will remain overweight into adulthood.[21, 22] The Bogalusa Heart Study reported recently that overweight children are more likely than normal-weight children to be offspring of parents with early CAD, and that overweight children develop adverse cardiovascular risk profiles at a rate higher than that seen in normal-weight adults.[23] In addition, a higher body weight in childhood[21] and early adulthood[4, 22] is associated with increased cardiovascular mortality and all-cause mortality in children and in adults under age 65.[4, 6, 24]

Although the increased association with other cardiovascular risk factors, including diabetes and hypercholesterolemia, may explain the increased incidence of CAD in obese patients, belief in a direct association between obesity and CAD is widespread. Our data support the hypothesis that obesity is independently linked with premature occurrence of AMI, and several recognized mechanisms support this observed link. Hyperinsulinemia, often present in obese patients, could explain the influence of obesity on premature development of CAD;[25, 26] obesity associated with hyperinsulinemia has been found to be a powerful predictor of CAD.[25] Because obesity is associated with increased plasminogen-activator inhibitor activity,[27] altered coagulation could also influence the link between obesity and premature AMI.[28] Two trials, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I)[29] and Third Thrombolytric trial of Eminase (anistreplase) in Acute Myocardial infarction (TEAM-3),[30] have linked reduced efficacy of thrombolytic therapy with higher body weight in patients with AMI. The link between obesity and premature AMI could also be related to hypertriglyceridemia,[31] which is present in many obese patients and is suggested to be an independent predictor of CAD.[31]

The importance of obesity management is underscored both by the recognition that weight reduction can favorably modify other cardiovascular risk factors[32] and by its proven association with reduced cardiac and total mortality.[33] In one observational study of 12 years' duration, intentional weight loss of 0.5 to 9.0 kg in overweight women with obesity-related disorders was associated with a 20% reduction in all-cause mortality.[33] Management of obesity is very challenging, however, and begins with the understanding that a combination of environmental and genetic factors contribute to the process.[34]

Clinical Implications

Our study demonstrates an independent association between obesity and premature onset of acute AMI. Coupled with the evidence of a growing worldwide epidemic of obesity, our observations give rise to grave concerns for future efforts to reduce death and disability from heart disease. Although both research and study of the management of obesity are in their infancy,[12, 13] our data suggest that obesity in younger adults should be treated with the same aggressiveness and attention as is given to the management of hyperlipidemia and hypertension.

Our analysis revealed that obese patients were more likely than normal-weight patients to receive primary reperfusion and adjunctive therapies, and had slightly lower in-hospital mortality and slightly better left ventricular ejection fractions at hospital discharge. The most likely explanation for these observations is that the obese patients were younger and thus received more aggressive care at the time of presentation. The greater use of these treatment strategies is likely to have resulted in slightly lower rates of in-hospital complications and in a nonsignificantly lower mortality rate, and is also the most likely explanation for the observed differences in ejection fraction. These observed treatment differences do not affect our primary observation that obese individuals present at a significantly younger age with AMI than nonobese individuals.

Limitations

Our study is limited in several respects. First, a small number of patients with AMI from Olmsted County may not have been included, as about 5% of local cardiac patients are treated at another facility. Second, our cohort may underestimate the magnitude of individual risk factors. The fact that obese patients in this study were predominantly male may have biased our observations, even though multivariate modeling did not suggest an interaction between gender and obesity. Third, because our population is more homogeneous than the U.S.

population as a whole, racial factors could affect generalizability of these findings. Finally, because we did not examine how changes in BMI after hospitalization might affect long-term outcome, we could be overestimating the influence of BMI in patients presenting with a second or third AMI, although the great majority of our patients were presenting with their index AMI and multivariate modeling did not suggest any interaction.

Conclusions

Our population-based study shows an independent association between overweight or obese status and the premature occurrence of AMI, but not with an increased incidence of in-hospital complications.

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