Multi-Vessel Disease in Metabolically Healthy Obese Patients Presenting with ST-Elevation Myocardial Infarction

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ABSTRACT **Background:** The extent and impact of obesity as an isolated risk factor for coronary artery disease is not clear since co-morbidities serve as confounders and may mask this association.

Objectives: To examine whether obesity is associated with extensive coronary artery disease among metabolically healthy patients presenting with ST-elevation myocardial infarction (STEMI) and to explore the outcomes according to body mass index (BMI).

Methods: We stratified STEMI patients who had a metabolically healthy phenotype and available weight and height data according to BMI: 18.5–25 kg/m² (lean), 25.01–30 kg/m² (overweight), and > 30 kg/m² (obese).

Results: Overall 381 patients were included, 42% lean, 41% overweight, and 17% obese. Patients with increased BMIs had higher levels of low-density proteins and triglycerides ($P < 0.05$). Obese patients presented with the lowest rates of multi-vessel disease (12.9% vs. 22.9% for overweight and 28% for lean). In a univariable analysis, obese patients were 60% less likely to be diagnosed with multi-vessel disease (odds ratio 0.4, 95% confidence interval 0.2–0.9, $P = 0.021$) compared to lean patients. The association remained significant in a multivariable model adjusted for baseline characteristics ($P = 0.029$). There were no differences in 30-day or long-term mortality (median follow-up 3.2 years) among the groups ($P > 0.1$ for all comparisons).

Conclusions: Metabolically healthy phenotype obesity was associated with lower rates of multi-vessel disease despite higher levels of triglycerides; however, this association did not translate into increased mortality.

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Obesity is an established risk factor for cardiovascular diseases [1], particularly coronary atherosclerosis [2]. The pathogenesis of coronary atherosclerosis is partially mediated by obesity-related co-morbidities [1] such as hyperlipidemia, hypertension, and diabetes mellitus [3,4]. Therefore, the direct effect of obesity on coronary artery disease (CAD) is still not completely clear [5]. Studies linking obesity and CAD have attempted to isolate a metabolically healthy phenotype [6,7], which is characterized by an obese population without the associated co-morbidities. However, conflicting results have been reported [6-10].

Clinical outcomes of these patients are a matter of debate as well. The obesity paradox, which refers to improved outcomes of patients with higher body mass index (BMI) [11], was not persistently found among metabolically healthy patients [12]. The variations in outcomes may be partially explained by the heterogeneous cohorts and the inconsistent definitions of metabolically healthy phenotypes [7,12]. To eliminate robust confounders and investigate the direct association between obesity and CAD we used strict criteria (specified below) to define the metabolically healthy phenotype. We examined whether obesity was associated with extensive CAD among metabolically healthy patients presenting with ST-elevation myocardial infarction (STEMI), and explored these outcomes according to BMI.

PATIENTS AND METHODS

STUDY POPULATION

Patients admitted from 2009 to 2016 to the Cardiac Intensive Care Unit at the Tel Aviv Sourasky Medical Center with the diagnosis of acute STEMI were retrospectively identified. First, we excluded patients with known components of the metabolic syndrome (i.e., patients with hypertension, diabetes mellitus, or hyperlipidemia). We further excluded patients without full data regarding height and weight. Finally, patients with additional undiagnosed metabolic disturbances (total cholesterol ≥ 240mg/dl, low density

lipoprotein ≥ 160 mg/dl, triglycerides ≥ 150 mg/dl, and hemoglobin A1C ≥ 6.5% at admission) were excluded. Thus, the final study population included metabolically healthy patients (i.e., patients without hypertension, diabetes mellitus, or hyperlipidemia). All patients were treated with primary percutaneous coronary intervention (PCI). Baseline demographics, cardiovascular history, clinical risk factors, treatment characteristics, laboratory results, and mortality data were retrieved from the hospital electronic medical records. All-cause mortality data (date, if occurred) are automatically updated in the hospital records from Israeli's social security agency via the Ministry of Health and can be retrieved by identification number. The study protocol was approved by the local institutional ethics committee.

STUDY DEFINITIONS

A metabolically healthy obese phenotype was defined as BMI > 30 without hypertension, diabetes mellitus, or hyperlipidemia [13].

We compared outcomes of obese (> 30 kg/m^2), overweight (25.01–30 kg/m^2), and lean (18.5–25 kg/m^2) individuals with STEMI. Outcomes were compared for all three study groups and for the obese vs. lean patient groups. BMI was calculated according to the formula: weight (kilograms)/height^2 (meters^2). Diagnosis of STEMI was established in patients with a typical chest pain history, diagnostic electrocardiographic changes, and serial elevation of cardiac biomarkers.

Significant CAD was defined as a stenosis of above 70% of the coronary lumen. Multi-vessel disease was defined as more than 1 vessel CAD with a narrowing of 50% or above. In addition, in-hospital outcomes were evaluated: systolic dysfunction (defined as ejection fraction < 50% according to echocardiography during the index admission), heart failure (left or right, defined according to Framingham Clinical Criteria), bleeding (defined according to BARC-2 criteria), acute kidney injury (defined according to KDIGO criteria), and other in-hospital procedural-related complications. Routine electrocardiogram tests during hospitalization were used to diagnose new-onset atrial fibrillation.

Echocardiographic measurements were made using the same equipment for each examination (iE33, Philips Medical Systems, Bothell, WA, USA) by a specialized operator and in accordance with the published guidelines of the American Society of Echocardiography. Echocardiographic evaluations of left ventricular ejection fraction were interpreted by a specialized physician according to the Simpson's method.

STATISTICAL ANALYSIS

Categorical variables were reported as numbers or percentages, and continuous variables were reported as means and standard deviations or as medians and interquartile ranges (IQRs). Continuous variables were tested for normal distribution using histograms and Q-Q Plots. Continuous variables were compared between groups using analysis of variance (ANOVA) or Mann-Whitney test and categorical variables were compared using Chi-square test or Fisher's exact test. The associations of BMI with multi-vessel CAD and atrial fibrillation were determined using logistic regression models. Odds ratio (OR) and 95% confidence interval (95%CI) were reported. The associations of BMI with all-cause mortality were determined and presented using a Cox survival model. Baseline patient characteristics were examined for the multivariable models. Variables which contributed significantly to the model were included according to the backward stepwise method. The final model of multi-vessel disease included age and prior myocardial infarction. The final model of atrial fibrillation included age. The final model of all-cause mortality included age, family history of ischemic heart disease, and creatinine. ANOVA was used for Post hoc analysis. A 2-tailed $P < 0.05$ was considered significant for all analyses. Missing data were handled with multiple imputations. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

STUDY POPULATION

The cohort consisted of 381 metabolically healthy patients who presented with STEMI and were treated by primary PCI. The majority were male (88.2%) and the mean age was 57.6 ± 12 years. The cohort consisted of 42% (n=161) lean patients (BMI 18.5–25 kg/m^2), 41% (n=156) overweight (BMI 25.01–30 kg/m^2), and 17% (n=64) obese (BMI > 30 kg/m^2). A non-significant trend for younger ages was noted inversely to BMI groups (mean age 56 years for obese vs. 57 years for overweight and 59 years for lean patients; $P = 0.089$). Mean levels of total cholesterol and low-density lipoproteins, and median levels of high-density lipoproteins, triglycerides, and hemoglobin A1C for the entire cohort were 165 ± 29 mg/dl, 107 ± 27 mg/dl, 39 (IQR 34–44 mg/dl), 76 (IQR 54–105 mg/dl), and 5.8 (IQR 5.4–6 %), respectively. Patients with increased BMIs had higher levels of low-density lipoproteins and triglycerides ($P < 0.05$). Levels of high-density lipoproteins, total cholesterol, or hemoglobin A1C did not differ significantly across the groups [Table 1]. When comparing lean and obese patients, the low-density lipoproteins were higher in the obese group but were not statistically significant. Triglyceride levels remained significantly higher in the obese group.

IN-HOSPITAL OUTCOMES

Obese patients demonstrated lower rates of multi-vessel disease according to coronary angiography (12.9% vs. 22.9% for overweight and 28% for lean; $P = 0.058$) and were more likely to develop new onset atrial fibrillation compared with other groups (9.4% vs. 1.9% for overweight and 3.7% for lean; $P = 0.035$). There were no differences in rates of other in-hospital complications, including heart failure, systolic dysfunction (ejection fraction < 50%), hemodynamic instability, bleeding, or hospitalization durations [Table 2]. In a univariable model, obese patients were 60% less

likely to be diagnosed with multi-vessel disease compared to lean patients (OR 0.4, 95%CI 0.2–0.9, $P = 0.021$). The association remained significant in a multivariable model adjusted for baseline characteristics ($P = 0.029$). Overweight patients did not demonstrate an increased risk for multi-vessel disease or atrial fibrillation compared to lean patients [Table 3]. When comparing obese vs. lean patients, multi-vessel disease was significantly more prevalent in the lean group and the difference in atrial fibrillation rates was only non-significantly higher in the obese group.

MORTALITY

The highest 30-day mortality rate was noted among obese patients (4.7% vs. 3.3% for overweight and 1.3% for lean); however, the difference was not statistically significant ($P = 0.306$). Over a median follow-up period of 3.2 years (IQR 2–4.7), 30 patients (7.9%) died. Although survival curves visually imply a higher trend for mortality among the obese compared to other BMI groups [Figure 1], the difference did not reach statistical significance ($P = 0.245$ for all three groups and 0.094 for obese vs. lean patients).

DISCUSSION

The main finding of the present study is that obesity with a metabolically healthy phenotype was associated with lower rates of multi-vessel disease despite higher levels of triglycerides.

The association between obesity with a metabolically healthy phenotype and CAD has been studied among several demographics [6-10]. A large observational study demonstrated

Table 1. Baseline characteristics according to body mass index

	BMI 18.5–25 kg/m² n=161	BMI 25.01–30 kg/m² n=156	BMI >30 kg/m² n=64	*P* value all groups	*P* value obese vs. lean
BMI, kg/m²	23.1 ± 1.5	27.1 ± 1.4	32.9 ± 2.5		
Age, years	59 ± 13	57 ± 12	56 ± 12	0.09	0.13
Male gender (%)	87.6	89.7	85.9	0.69	0.74
Prior myocardial infarction (%)	5	8.3	7.8	0.47	0.53
Family history of IHD (%)	20.5	21.2	31.3	0.19	0.09
Smoker (%)	62.1	60.3	51.6	0.38	0.15
Creatinine, mg/dl	1.06 ± 0.2	1.06 ± 0.22	1.07 ± 0.23	0.74	0.91
Hemoglobin, g/dl	14.3 ± 1.4	14.7 ± 1.4	14.8 ± 1.3	0.01	0.03
Creatinine phosphokinase, mg/dl	954 (410–1834)	932 (399–2015)	853 (439–1974)	0.98	0.99
Total cholesterol, mg/dl	164 ± 30	163 ± 28	171 ± 32	0.14	0.2
LDL, mg/dl	104 ± 27	108 ± 27	115 ± 28	0.03	0.053
HDL, mg/dl	41 (34–42)	39 (34–44)	37 (32–42)	0.13	0.1
Triglycerides, mg/dl	70 (52–103)	77 (52–104)	91 (64–112)	0.02	0.01
Hemoglobin A1C (%)	5.7 (5.5–5.9)	5.8 (5.4–6)	5.8 (5.4–6.1)	0.85	0.87

BMI = body mass index, HDL = high-density lipoprotein, IHD = ischemic heart disease, LDL = low-density lipoprotein

Table 2. In-hospital characteristics and complications according to body mass index

	BMI 18.5–25 (kg/m²)	BMI 25.01–30 (kg/m²)	BMI > 30 (kg/m²)	*P* value all groups	*P* value obese vs. lean
Time to perfusion, minutes	150 (105–390)	150 (92–300)	150 (105–360)	0.58	0.7
Multi-vessel disease, %	28	22.9	12.9	0.06	0.02
Systolic dysfunction (EF < 50%), %	38.3	43.1	34.6	0.54	0.64
Heart failure, %	8.1	7.1	12.5	0.41	0.3
Intra-aortic balloon pump/inotropes, %	1.2	2.6	4.7	0.23	0.14
Atrial fibrillation, %	3.7	1.9	9.4	0.04	0.11
Bleeding, %	3.7	2.6	3.1	0.92	1
30-day mortality, %	1.3	3.3	4.7	0.31	0.12

BMI = body mass index, EF = ejection fraction

Table 3. Associations between body mass index and outcomes referenced to lean patients

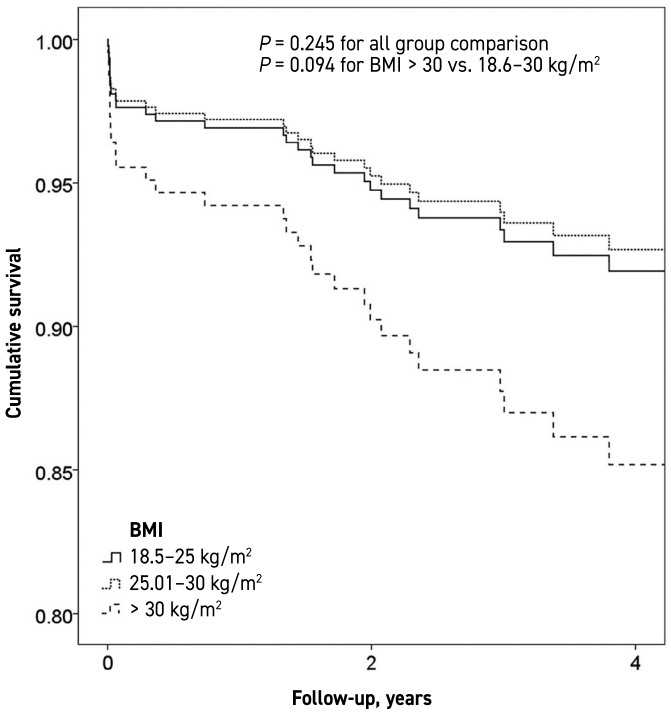
		Univariable		Multivariable*	
		OR (95%CI)	*P* value	OR (95%CI)	*P* value
Multi-vessel disease (compared to BMI 18.5–25 kg/m²)	**Overweight**	0.8 (0.5–1.3)	0.3	0.8 (0.5–1.4)	0.44
	Obese	0.4 (0.2–0.9)	0.02	0.4 (0.2–0.9)	0.03
Atrial fibrillation (compared to BMI 18.5–25 kg/m²)	**Overweight**	0.5 (0.1–2.1)	0.34	0.6 (0.1–2.5)	0.47
	Obese	2.7 (0.8–8.6)	0.1	2.8 (0.7–2.5)	0.15
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
All-cause mortality (compared to BMI 18.5–25 kg/m²)	**Overweight**	0.9 (0.4–2.1)	0.81	0.9 (0.4–2.4)	0.96
	Obese	1.9 (0.8–4.7)	0.16	2.3 (0.8–6.4)	0.1

BMI = body mass index
*Adjusted for selected parameters from Table 1 according to the backward stepwise method:
Multi-vessel disease - adjusted forage, prior myocardial infarction
Atrial fibrillation = adjusted forage
All-cause mortality = adjusted for age, family history of ischemic heart disease, creatinine
95%CI = 95% confidence interval, HR = hazard ratio, OR = odds ratio

an association between obesity and CAD [6]. The opposing results between these findings and the current study may possibly be explained by the heterogeneous cohort in the former. An epidemiological study design may introduce potential confounders that cannot be accounted for [14]. Of note, there was a relatively low rate of prior myocardial infarction and low average age in our cohort. Since obesity might impose a more sedentary lifestyle [15] and have different effects at advanced ages, our cohort may be subject to certain selection biases. An additional explanation for the inconsistency with previous studies is the non-uniform definition of a metabolically healthy patient [7,12]. We analyzed this association using relatively stringent criteria. To augment the removal of potential confounders, not only patients with any known obesity-related morbidities were excluded, but also those with undiagnosed metabolic abnormalities.

It had been suggested that obesity increases atherosclerotic burden [12], yet several studies have failed to demonstrate an association between obesity and CAD [7,8]. To the best of our knowledge, our study is the first to show that higher BMIs portend a protective effect against CAD compared with lower BMIs. The relationship between adiposity and CAD is not fully understood. One of several mechanisms thought to mediate between the two involves hormonal pathways. Adiponectin, a hormone secreted from adipose tissue, may provide a cardio-protective effect during myocardial infarction [16]. Another possible explanation may be that physicians think obese patients are more prone to cardiovascular co-morbidities and therefore emphasize the importance of a healthy lifestyle. Nonetheless, there was no difference in the rate of smokers, and dietary data were was not collected in our registry. A third possible mechanism involves cardiac adaptation of athletes. Trained individuals develop enhanced cardiovascular capacity [17], which may potentially extend the interval between

Figure 1. Cox survival curves according to body mass index (BMI) category



symptom onset and presentation at the emergency department. In addition, it had been shown that athletes exhibit a higher coronary calcium score [18]. Although it is more likely that lean rather obese patients are more athletic, physical activity is not documented in our registry.

Despite the differences in prevalence of multi-vessel disease, mortality rates did not vary significantly across the study groups in the current cohort. The obesity paradox described for STEMI

patients [19] has also been found among metabolically healthy populations [20]. However, a large meta-analysis failed to clearly demonstrate better outcomes for acute coronary syndrome (ACS) patients with increased BMIs [21]. Various factors may influence outcomes according to BMI. Obesity was hypothesized to affect cardiac remodeling [22], and in the setting of ACS, obesity was associated with decreased rates of malignant ventricular arrhythmias [23]. Conversely, clopidogrel has been shown to provide reduced platelet inhibition among obese patients [24]. Obese patients are thought to be generally prone to receive sub-therapeutic dosages [25]. Although a trend for higher mortality among the obese in the present cohort can be seen by the survival curves [Figure 1], adjusted analyses failed to prove such unfavorable outcomes. Our study may have been underpowered for the evaluation of this complex relation, perhaps due to low rates of adverse outcomes in a population without major cardiovascular risk factors.

LIMITATIONS

A retrospective study is subjected to the known inherent biases of its design. Our study may have been underpowered for assessing mortality. BMI measurements are limited in distinguishing lean body mass from adipose tissue. However, data on alternative estimations, which may better represent obesity such as hip-to-waist or hip-to-height ratios, were not documented in our registry. In addition, our database had no information regarding additional procedural characteristics, specifically CAD anatomical scores, the distribution of vessels, the need for multi-vessel intervention, and the utilization of drug eluting stents. Finally, the current results are registry-based, in which angiographic data were collected prospectively based on the interpretation of the interventional cardiologist during the index admission and were not reviewed by an independent committee.

CONCLUSIONS

Obesity with a metabolically healthy phenotype is associated with lower occurrence of multi-vessel disease in STEMI patients. Nonetheless, we recognize that the trend for younger obese patients may alternatively signify earlier plaque rupture and conclusions should not be inferred to the general population.

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