original article

Absence of obesity paradox in Saudi patients admitted with acute coronary syndromes: insights from SPACE registry

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BACKGROUND AND OBJECTIVES: To describe the distribution of body mass index (BMI) and its relationship with clinical features, management, and in-hospital outcomes of patients admitted with acute coronary syndromes (ACS).

DESIGN AND SETTINGS: The Saudi Project for Assessment of Coronary Events is a prospective registry. ACS patients admitted to 17 hospitals from December 2005–2007 were included in this study.

METHODS: BMI was available for 3469 patients (68.6%) admitted with ACS and categorized into 4 groups: normal weight, overweight, obese, and morbidly obese.

RESULTS: Of patients admitted with ACS, 72% were either overweight or obese. A high prevalence of diabetes (57%), hypertension (56.6%), dyslipidemia (42%), and smoking (32.4%) was reported. Increasing BMI was significantly associated with diabetes, hypertension, and hyperlipidemia. Overweight and obese patients were significantly younger than the normal-weight group (P=.006). However, normal-weight patients were more likely to be smokers and had 3-vessel coronary artery disease, worse left ventricular dysfunction, and ST elevation myocardial infarction. Glycoprotein IIb-IIIa antagonists were used significantly more in overweight, obese, and morbidly obese ACS patients than in normal-weight patients ($P \leq .001$). Coronary angiography and percutaneous intervention were reported more in overweight and obese patients than in normal-weight patients ($P \leq .001$). In-hospital outcomes were not significantly different among the BMI categories.

CONCLUSION: High BMI is prevalent among Saudi patients with ACS. BMI was not an independent factor for in-hospital outcomes. In contrast with previous reports, high BMI was not associated with improved outcomes, indicating the absence of obesity paradox observed in other studies.

Obesity is increasing in prevalence worldwide and has reached epidemic proportions in many countries. Two-thirds of the US population is overweight or obese.[1,2] According to the most recent National Health and Nutrition Examination Survey , 68% of adult men and women are overweight or obese.[3,4] The EUROASPIRE III survey revealed that obesity (body mass index [BMI] >30) was highly prevalent in coronary heart disease patients across all 22 participating countries, reaching an overall prevalence of 35%.[5] In the Saudi population, the prevalence of overweight and obesity was 72.5%, which is similar to that in the United States.[6] Obesity is known to be associated with increased morbidity and mortality,[7,8] and it has been predicted that if the current obesity trends continue, the negative effects of increasing BMI will overwhelm the positive effects of decline in smoking.[9] The aim of our study was to evaluate the impact of BMI in unselected Saudi patients admitted with acute coronary syndrome (ACS) in relation to demographic data, clinical presentation, medication, use of angiography and revascularization procedures, and in-hospital outcomes.

METHODS

The Saudi Project for Assessment of Coronary Events (SPACE) registry was a prospective study conducted in 17 hospitals from 5 major regions in Saudi Arabia. The details of the study were outlined previously.[10,11] In summary, between December 2005 and December 2007, 5056 patients admitted with ACS were enrolled. All patients with ACS had a final diagnosis of ST elevation myocardial infarction (STEMI), non–ST segment elevation myocardial infarction (NSTEMI), and unstable angina. Diagnosis of different types of ACS and definitions of data variables were based on the definitions of the American College of Cardiology.[12] Data were collected for the following variables: patient demographics, medical history, provisional diagnosis on admission and final discharge diagnosis, investigations, medical therapy, use of cardiac procedures and interventions, in-hospital outcome, and mortality. BMI was calculated as weight in kilograms divided by the square of height in meters. Patients were categorized according to the World Health Organization classification13 into 4 groups: underweight or normal weight, BMI <25; overweight, BMI 25–29.9; obese, BMI 30–39.9; and morbidly obese, BMI >40.

Statistical analysis

Categorical data were summarized with absolute numbers and percentages. Continuous data were summarized with means and standard deviations or median and interquartile range. Comparisons among different BMI groups were performed using chi-square test for categorical variables and analysis of variance or Kruskal–Wallis test for continuous variables. To study the relationship of mortality with BMI and other risk factors, a multiple logistic regression model was used. The odds ratio estimates and corresponding 95% confidence intervals were obtained using a multiple logistic regression model. All analyses were performed using SAS/STAT software, version 9.1.3 (SAS Institute, Cary, NC, USA).

RESULTS

Study population

In total, 5056 consecutive patients were enrolled in the SPACE registry. The data required for this study were available for 3469 ACS patients (68.6%), who were classified according to their BMI into 4 groups as shown in **Table 1**. Of the ACS patients included in the study, 72% were either overweight or obese.

Demographics and clinical characteristics

Table 1 depicts the baseline clinical characteristics of our cohort. Overweight, obese, and morbidly obese patients were more likely to be younger, have diabetes, hypertension, hyperlipidemia, and a history of ischemic heart disease and were less likely to be smokers compared to the normal-weight BMI group ($P<.05$). The median cholesterol and low-density lipoprotein cholesterol values showed no relationship with BMI, while the median fasting glucose levels and triglyceride levels were significantly associated with higher BMI.

ACS presentation and management

The normal-weight patients were more likely to present with atypical chest pain than the higher-BMI patients (P=.003). STEMI patients represented 41.2% of the study population. The increased BMI patients were more likely to present with NSTEMI, while the normal BMI group tended to present with STEMI ($P\leq.001$). A steady increase in the prevalence of NSTEMI was observed with increasing weight, and a steady increase in STEMI was observed with decreasing weight. No differences were recorded in heart rate, systolic blood pressure, and Killip class among the groups. In STEMI patients, BMI did not appear to influence the likelihood of receiving reperfusion therapy. BMI showed no relationship with either door-to-needle time or door-to-balloon time.

Medications

Table 2 depicts the in-hospital medications that were administered to the study participants. Similar proportions in each group were given aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), and thrombolytics. The high-weight groups were more likely to be treated with angiotensin receptor blockers and glycoprotein IIb-IIIa inhibitors than those in the normal-weight group ($P<.001$).

Procedures

Patients in the normal-weight group were more likely to have moderate-to-severe left ventricular (LV) systolic dysfunction ($P<.001$). Patients in the overweight, obese, and morbidly obese categories underwent significantly more cardiac catheterization procedures compared to the normal-weight group ($P\leq.001$). Three-vessel coronary artery disease (CAD) was less prevalent in the overweight and obese groups compared to the normal-weight group ($P\leq.001$). Patients in the overweight and obese groups undergoing percutaneous coronary intervention (PCI) ($P\leq.001$) and coronary stenting ($P\leq.002$) were more in number than in the normal-weight group (**Table 2**).

In-hospital outcomes

In-hospital outcomes were similar among the 4 BMI groups (**Table 3**). Patients who were overweight or

Table 1. Clinical characteristics of ACS patients according to BMI.

Variable	BMI <25 (N=969, 28%)	BMI 25-29 (N=1419, 41%)	BMI 30-39.9 (N=762, 22%)	BMI ≥40 (N=319, 9%)	*P*
Age mean (SD) (y)	59.1 (14.2)	57.6 (12.4)	57.6 (12.4)	56 (12.1)	.006
Male (%)	82.9	81.7	72.4	55.8	<.001
Saudi (%)	77.1	82.3	84.0	86.2	<.001
Diabetes (%)	52.2	58.2	60.0	62.7	<.001
Hypertension (%)	50	52.8	65.2	73.4	<.001
Dyslipidemia (%)	34.2	40.7	48.2	58.9	<.001
Current smoking (%)	37.9	32.5	27.8	26.5	<.001
Prior CAD (%)	38.7	45.6	49.4	49.5	<.001
Prior CABG (%)	5.2	6.2	4.9	6.0	.706
Prior CHF (%)	20.8	21.5	22.8	22.9	.850
Prior PAD (%)	9.9	8.8	7.5	8.1	.359
Prior CVA (%)	8.4	5.5	5.38	5.3	.047
HR >100/min (%)	14.2	13	13.14	9.1	.134
SBP <90 mm Hg	3.31	2.83	2.50	1.0	.156
Atypical chest pain (%)	4	2.7	2.49	5.3	.003
Killip class >1 (%)	20.8	21.5	22.2	22.9	.85
STEMI ACS	46.75	42.28	36.75	29.78	<.001
NSTEMI ACS	53.2	57.72	63.25	70.22	<.001
Cholesterol median (IQR)	4.4	4.4	4.4	4.2	.656
LDL median (IQR)	2.8	2.7	2.7	2.6	.196
Triglyceride median (IQR)	1.4	1.5	1.6	1.6	<.001
Fasting glucose median (IQR)	6.4	6.6	6.8	7	.003
LV ejection fraction <35% (%)	40.1	34.6	32.7	23.6	<.001

BMI: Body mass index, ACS: acute coronary syndromes, CAD: coronary artery disease, CABG: coronary bypass surgery, CHF: congestive heart failure, PAD: peripheral vascular disease, CVA: cerebrovascular disease, SBP: systolic blood pressure, STEMI: ST elevation myocardial infarction, NSETMI: non–ST elevation myocardial infarction, LV: left ventricle, LDL: low-density lipoprotein, IQR: interquartile range.

obese had similar in-hospital adverse events and mortality compared to normal-weight patients.

Multiple logistic regression analysis

Multiple logistic regression analysis was carried out for the predictors of in-hospital mortality (**Table 4**). The independent variables significantly associated with mortality were age, beta-blockers, ACEI, statin, heart failure, and Killip class. BMI was not an independent predictor of in-hospital mortality.

DISCUSSION

Obesity is associated with numerous adverse cardiovascular effects. These include increased risk of hypertension, type 2 diabetes mellitus, LV hypertrophy, dyslipidemia, heart failure, atrial fibrillation, stroke, sudden cardiac death, endothelial dysfunction,[14] and premature occurrence of myocardial infarction.[15]

A meta-analysis of 21 long-term studies that followed more than 300 000 patients identified a 45% increase in coronary heart disease in patients who were overweight or obese, even after adjustments for blood pressure and cholesterol levels.[16] It has also been shown that obesity confers an elevated risk of ACS; each unit increase in BMI was associated with a 5% and 7% higher risk of ACS among women and men, respectively.[17] In patients with angiographically confirmed CAD, BMI is independently associated with unstable angina

Table 2. In-patient management of ACS patients according to BMI.

Variable	BMI <25 (N=969, 28%)	BMI 25-29 (N=1,419, 41%)	BMI 30-39.9 (N=762, 22%)	BMI ≥40 (N=319, 9%)	*P*
Inpatient medications of the study population (%)					
Aspirin	98.	98.4	98.7	98.7	.852
Clopidogrel	87.5	87.0	89.6	88.0	.349
Beta-blockers	84.1	86.2	86.9	85.2	.361
ACEI	71.7	72.8	70.8	71.4	.781
ARB	4.4	5.0	9.5	8.2	<.001
Statin	97	96.8	96.4	93.7	.037
Heparin	83.01	84.21	84.3	81.8	.688
GPIIb–IIIa inhibitors	26.9	31.6	37.0	30.4	<.001
STEMI management					
Thrombolytics (%)	50.4	52.8	53.1	45.4	.488
Door-to-needle time <30 min (%)	23.8	25.5	26.0	25.0	.977
Door-to-balloon time <90 min (%)	25.9	30.5	35.1	63.6	.101
Discharge medications of the study population (%)					
Aspirin	97.1	97.5	98.1	97.7	.64
Clopidogrel	70.8	77.0	74.6	70.4	.004
Beta-blockers	88.8	80.7	89.7	86.0	.084
ACEI	72.3	74.9	70.3	71.1	.113
ARB	6.5	6.5	11.4	10.7	<.001
Statin	95.6	97.0	96.1	96.4	.397
Coronary angiography (%)					
Total coronary angiography	61.7	67.5	74.2	71.8	<.001
LMS	7.0	4.7	4.8	3.5	.104
SVD	27.0	30.9	32.6	35.4	.218
DVD	20.5	23.5	23.4	15.7	.046
TVD	38.2	32.7	29.6	24.9	<.001
PCI	29.3	35.3	38.8	36.7	.002
CABG	9.1	7.9	9.9	6.6	.155

ACE: Angiotensin converting enzyme inhibitors, ACS: acute coronary syndromes, ARB: angiotensin receptor blockers, GPIIa-IIb inhibitors: glycoprotein IIb-IIIa inhibitors, STEMI: ST elevation myocardial infarction, LMS: left main stem disease, SVD: single-vessel disease, DVD: double-vessel disease, TVD: triple-vessel disease, PCI: percutaneous intervention, CABG: coronary bypass surgery, CHF: congestive heart failure.

Table 3. In-hospital outcomes (%).

Variable	BMI <25 (N=969, 2%)	BMI 25-29 (N=1,419, 41%)	BMI 30-39.9 (N=762, 22%)	BMI ≥40 (N=319, 9%)	*P*
Major bleeding	1.34	1.41	1.05	1.57	.863
Stroke	1.4	0.85	0.79	1.88	.336
Re-infarction	1.34	1.06	0.79	2.19	.242
CHF	9.9	9.59	10.10	10.66	.861
Cardiogenic shock	4.75	4.79	3.67	3.45	.53
Death	2.48	2.89	2.62	3.76	.644

CHF: Congestive heart failure

Table 4. Multiple logistic regression analysis for predictors of mortality in patients with ACS.

Factor	OR	95% CI	*P*
Male gender	0.752	(0.44-1.28)	.296
Age	1.049	(1.02-1.07)	<.001
Diabetes mellitus	1.24	(0.60-2.52)	.514
Hypertension	1.965	(0.95-4.07)	.069
Dyslipidemia	0.965	(0.49-1.87)	.917
Smoking	1.179	(0.60-2.31)	.6317
BMI <25 (normal/ underweight) reference			
BMI 25-29.9 (overweight)	1.399	(0.768-2.55)	.272
BMI 30-39.9 (obese)	1.252	(0.616-2.54)	.534
BMI ≥40 (very obese)	1.307	(0.547-3.11)	.546
Atypical chest pain	0.854	(0.11-6.62)	.879
Coronary angiography	0.896	(0.47-1.68)	.653
Clopidogrel	0.655	(0.31-1.35)	.2536
Beta-blockers	0.56	(0.32-0.96)	.0354
ACEI	0.57	(0.34-0.94)	.0274
Statin	0.34	(0.15-0.76)	.0088
CHF	4.463	(2.53-7.84)	<.001
Killip class >1	0.354	(0.20-0.63)	<.001

BMI: Body mass index, ACEI: angiotensin-converting enzyme inhibitors, CHF: congestive heart failure, CI: confidence interval, ACS: acute coronary syndromes.

and myocardial infarction even after adjusting for other risk factors.[18]

BMI is an important health parameter and has a role in patient management, such as lifestyle modification; however, it was not available for 31% of patients with ACS in the SPACE registry. A high prevalence of overweight and obesity has been reported in the Saudi population. Al-Nozha et al reported a prevalence of 72.5% of overweight and obesity among the Saudi population.[6] A high prevalence was also reported in another recent study from the eastern province in Saudi Arabia, where 195 874 people were screened and the overall prevalence of overweight and obesity was 78.9%.[19] The prevalence of overweight and obesity in Saudi patients presenting with ACS has not been studied previously. Our study revealed a high prevalence of both conditions among the studied population; 72% of patients admitted with ACS for whom BMI was available were found to be either overweight or obese. This finding is in agreement with the results from the CRUSADE initiative and from the national cardiovascular registry (NCDR) in the United States. In the CRUSADE initiative involving 80 845 patients with NSTEMI, 70.5% of patients were classified as overweight or obese.[20] In the recently reported NCDR involving 50 149 patients with STEMI, three-fourths of the patients were overweight or obese.[21] Additionally, patients admitted with ACS who were overweight or obese tended to be younger than normal-weight patients. This observation was similar to the results of other ACS registries.[20-27] This is due to the fact that obesity appears to accelerate established CAD, leading to premature occurrence of myocardial infarction.[15]

Our study showed that normal-weight ACS patients, in addition to being older, were more likely to have a history of smoking and 3-vessel CAD (revealed by angiography) and more significant LV systolic dysfunction. It is well known that older age and smoking are independent risk factors for ACS regardless of the weight status. In patients admitted with ACS, an increasing trend was observed with increasing prevalence of risk factors (hypertension, diabetes, and hyperlipidemia) because the BMI increases across all the BMI categories. The prevalence of diabetes was extremely high in the studied population (57%), with a higher prevalence in overweight, obese, and very obese patients (58%, 60%, and 63%, respectively) compared to normal-weight patients (52%). The prevalence of diabetes in our study is the highest among the reported studies.[15,20-26] This finding might be due to the high prevalence of diabetes among the Saudi population.[28] A history of CAD was also strongly associated with rising BMI. The same relationship, but to a lesser extent, was found with cerebrovascular disease. The fasting glucose and triglyceride levels were more elevated in patients in the higher BMI categories, reflecting the relationship of obesity with impaired glucose tolerance, metabolic syndrome, diabetes, and dyslipidemia.

Overweight and obese patients were more likely to have NSTEMI, while normal-weight patients were more likely to present with STEMI. These findings were in contrast to what was observed in a Portuguese ACS registry of 14 391 patients in which there were no differences in the prevalence of STEMI and NSTEMI in the high- and low-BMI groups.[26]

Most patients received medications according to ACS guidelines.[29,30] Saudi Arabia is developing in terms of its heath care system, and the drugs needed for ACS are available in most of the centers. Our study reflected the proper utilization of drugs for most cases. This could explain the observed low mortality among patients with ACS in our study. Interestingly, there was no significant relationship between the use of most medications and BMI, which may indicate that our health care professionals are treating ACS cases equally, irrespective of their weight. Glycoprotein IIb-IIIa antagonists use was significantly greater in overweight, obese, and morbidly obese patients. This could be explained by the fact that there is a higher prevalence of diabetes and higher rates of PCI among these patients, for whom the evidence for anti-platelet use is stronger.[31]

Cardiac catheterization is not available in all hospitals in Saudi Arabia, yet a significant fraction of the study population underwent this procedure. This is because the study participants were recruited mostly from tertiary cardiac centers. Three-vessel coronary disease and LV systolic dysfunction were more prevalent in the normal/underweight BMI category compared to other BMI categories. However, more patients in the overweight and obese groups underwent coronary angiography and PCI compared to the underweight and normal-weight groups, similar to previously reported studies from the United States and Europe.[20,22,24]

According to the "obesity paradox," overweight and obese patients with established cardiovascular disease seem to have a more favorable prognosis than leaner patients despite clustering of risk factors in the former.[32,33] This observation has been reported in previous ACS registries from the United States, Europe, Japan, Portugal, and Israel.[20,22,25-27] In a meta-analysis of 40 studies with a mean follow-up of 3.8 years that included 250 152 patients with established CAD, outcomes for cardiovascular and total mortality were better for overweight and mildly obese groups compared to normal-weight patients. Adjustment for confounding factors did not change the findings.[34] The reasons behind this surprising paradox are unclear. Possible explanations include presentation at a younger age for obese patients with cardiovascular disease; more metabolic reserves for obese patients, who can thus better tolerate the catabolic stress of myocardial ischemia, lower levels of circulating atrial natriuretic peptides, and attenuated sympathetic nervous system and renin–angiotensin responses; and greater toleration of higher doses of cardioprotective medications by obese individuals.[14,33] The more aggressive strategy of treatment in overweight and obese patients, including increased use of medications, coronary angiography, and PCI, has been proposed to explain the improved outcome in patients with ACS.[20,22,24] Conversely, weight loss due to chronic disease may serve as a confounding variable, worsening outcomes in lower-weight patients. Other investigators have reported a U-shaped relationship between BMI and mortality in ischemic heart disease, with higher mortality in underweight and extremely obese patients and lower mortality in overweight and moderately obese patients.[21,27] In the recently reported NCDR from the United States, there was higher adjusted in-hospital mortality in the extremely obese patients compared to other weight categories. In contrast, and despite the more aggressive treatment of the high-BMI group, our study did not show evidence of an obesity paradox; no significant differences were reported in the outcomes regardless of the BMI, which is in agreement with a previous observation from the Middle East.[27] This could be due to ethnicity differences between the Middle Eastern and Western societies, and might also be explained by the younger age group in our study population (across all BMI categories) and the narrower age gap between normal-weight and overweight and obese patients in our study population compared to other reported studies, in which the age difference was larger.[19,24-26,28-31] In addition, this might also be due to the high prevalence of diabetes and other risk factors among all BMI groups, which would decrease the differences in the outcomes between the normal-weight and high-BMI groups. Based on multiple logistic regression analysis, BMI was not an independent predictor of mortality in this study; this is in agreement with an earlier study from the Middle East.[23]

Several limitations exist in our study. First, the use of BMI is limited by the fact that it cannot discriminate between fat mass and lean mass; the cutoff values may be different for specific ethnic populations, and BMI does not reflect body fat distribution, such as abdominal fat. Therefore, BMI may not be the best measure of cardiovascular risk.[34] The combination of BMI and waist circumference may offer a better method for assessing obesity than BMI alone. Second, our study was limited to short-term in-hospital outcome. Third, as with most other registries, hospital enrollment was voluntary; thus, the study results may not be a representative of clinical practice in all hospitals in the country. In addition, hospitals that participated in the registry could be more enthusiastic about adherence to guidelines and quality improvement initiatives. However, the wide geographic distribution of several hospitals from different health care sectors in our study provides a reasonable overall representation of ACS care. Fourth, there was an inherent selection bias because of the observational nature of the study design. Finally, the sample size in the extremely obese BMI group was small.

In conclusion, this study revealed a high prevalence of obesity among patients with ACS. Moreover, we did not observe the obesity paradox in our study population in Saudi Arabia. Primary prevention programs for obesity are sorely needed at the national level. More studies with longer follow-up periods that incorporate both BMI and waist circumference or BMI and waist-to-hip ratios are needed.[35,36]

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