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Reality of obesity paradox: Results of percutaneous coronary intervention in Middle Eastern patients

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Abstract

Objective: The aim of this study was to assess the baseline clinical characteristics, coronary angiographic features, and adverse cardiovascular events during hospitalization and at 1 year of follow-up in obese patients compared with overweight and normal/underweight patients.

Methods: A prospective, multicenter study of consecutive patients undergoing percutaneous coronary intervention was performed.

Results: Of 2425 enrolled patients, 699 (28.8%) were obese, 1178 (48.6%) were overweight, and 548 (22.6%) were normal/underweight. Obese patients were more likely to be female and to have a higher prevalence of diabetes, hypertension, hypercholesterolemia, or previous percutaneous coronary intervention. Acute coronary syndrome was the indication for percutaneous coronary intervention in 77.0% of obese, 76.4% of overweight, and 77.4% of normal/underweight patients. No significant differences in the prevalence of multi-vessel coronary artery disease or multi-vessel percutaneous coronary intervention were found among the three groups. Additionally, no significant differences were found in stent thrombosis, readmission bleeding

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rates, or cardiac mortality among the three groups during hospitalization, at 1 month, and at 1 year.
Conclusion: The major adverse cardiovascular event rate was the same among the three groups throughout the study period. Accordingly, body mass index is considered a weak risk factor for cardiovascular comorbidities in Arab Jordanian patients.

Keywords
Cardiovascular disease, obesity, obesity paradox, Middle Eastern patients, percutaneous coronary intervention, major adverse cardiovascular events

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Introduction

Cardiovascular disease is the leading cause of death in the Middle East.[1] Obesity, an established cardiovascular risk factor,[2] is highly prevalent in the general population in the region[3] and among patients admitted with acute coronary syndrome (ACS).[4] Obese patients admitted with ACS or those who undergo percutaneous coronary intervention (PCI) may have a more favorable outcome than underweight or normal patients.[5] The potential presence of the "obesity paradox" and its impact on 1-year outcomes in Middle Eastern patients who undergo PCI for ACS or stable coronary disease has not been addressed by large ACS or PCI registries.[4,6] The two regional studies that evaluated outcomes in obese patients reached conflicting conclusions about the in-hospital event rates, and neither evaluated the outcome at 1 year.[7,8] The first showed no difference in the in-hospital outcome across body mass index (BMI) groups among patients admitted with ACS.[7] The other demonstrated better in-hospital outcomes in overweight and obese patients who underwent elective PCI.[8] Our study is unique in that it is the first to evaluate the short- and long-term outcomes of patients who underwent PCI in the Middle East, a region in the world that is not well represented among cardiovascular interventional studies. Therefore, this study was performed to assess the baseline clinical characteristics and coronary angiographic features and the adverse cardiovascular events during hospitalization, at 1 month, and at 1 year after discharge in obese patients compared with those in overweight and normal/underweight patients using data from the recently completed first Jordanian PCI Registry (JoPCR1).

Methods

Design and setting

This study was a prospective, multicenter, observational study involving consecutive patients who underwent PCI for ACS or stable coronary disease in 12 tertiary care hospitals in Jordan from January 2013 to February 2014. The methods were extensively explained in previous reports.[9,10]

Data collection and measurement

Briefly, a case report form was used to record data at hospital admission, at discharge, and at 1 and 12 months of follow-up. Data were collected during follow-up clinic visits or phone calls to the patient, household relative, or primary care physician. The patients' clinical characteristics were collected through a review of their medical records. The baseline data included clinical, laboratory, electrocardiographic, echocardiographic, and coronary angiographic features. BMI was calculated according to the standard formula (body weight [kg]/height [m]^2). Weight and height were measured as early as possible after hospital admission and when the clinical situation of each patient was stable enough to allow these measurements. Details of the PCI procedures and in-hospital complications were documented. All PCI procedures were performed according to current standard guidelines. The arterial access site, antiplatelet therapy, and type of stent used were at the operator's discretion.

ACS was classified as acute ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation ACS (NSTEACS), which included non-STEMI and unstable angina. Stable coronary disease included chronic stable angina and silent ischemia.

Clinical profiles, coronary angiographic features, and periprocedural complications were compared among three groups of patients according to BMI: obese (BMI of $\geq$30 kg/m^2), overweight (BMI of 25–29.9 kg/m^2), and normal/underweight (BMI of $<$25 kg/m^2). We also compared the incidence of adverse cardiovascular events including cardiac mortality, stent thrombosis, major bleeding events, and readmission for patients with heart failure, with ACS, and who underwent coronary revascularization among the three groups up to 1 year of follow-up. Cardiac mortality was defined as any death not attributed to a clear non-cardiac cause. Stent thrombosis, definite or probable, was defined according to the Academic Research Consortium definition.[11] Major bleeding events were defined according to the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) study definition and included intracranial hemorrhage, retroperitoneal bleeding, a $\geq$12% decrease in hematocrit from baseline, any red blood cell transfusion when the baseline hematocrit was $\geq$28%, or any transfusion when the baseline hematocrit was $<$28% with witnessed bleeding.[12] The study was approved by the Institutional Review Board of each participating hospital, and patients provided written informed consent.

Statistical analysis

IBM SPSS Statistics 20 (IBM Corp., Armonk, NY, USA) was used for data entry and analysis. Data are described using means and percentages. The chi-square test was used to assess differences in proportions among the three groups, and one-way analysis of variance was used to assess differences in means among the three groups. A binary logistic regression was used to assess differences in the rates of stent thrombosis, major bleeding, and cardiac mortality during the index hospitalization, at 1 month, and at 1 year among the three groups after adjusting for other variables. A P-value of $<$0.05 was considered statistically significant.

Results

Sample characteristics

The registry enrolled 2425 consecutive patients who underwent PCI, including 1857 (76.6%) with ACS and 568 (23.4%) with stable coronary disease. The BMI (mean $\pm$ standard deviation) was 28.5 ± 4.5 kg/m^2. The study population comprised 699 (28.8%) obese, 1178 (48.6%) overweight, and 548 (22.6%) normal/underweight patients.

The baseline demographic characteristics and risk factor profiles in the three groups

Table 1. Baseline features in three groups of patients stratified by BMI.

Clinical feature	BMI ≥30 kg/m^2 n = 699	BMI 25.0–29.9 kg/m^2 n = 1178	BMI <25 kg/m^2 n = 548	P
Age (years)	57.8 ± 10.7	58.3 ± 10.7	59.3 ± 11.4	0.06
Female	222 (31.8)	190 (16.1)	88 (16.1)	<0.001
Hypertension	484 (69.2)	715 (60.7)	312 (56.9)	<0.001
Hypercholesterolemia	382 (54.6)	584 (49.5)	218 (39.8)	<0.001
Current cigarette smoking	270 (38.6)	517 (43.9)	268 (48.9)	0.003
Family history of premature CVD	304 (43.5)	465 (39.5)	188 (34.3)	0.004
Chronic renal disease	22 (3.1)	24 (2.0)	23 (4.2)	0.14
eGFR of <60 mL/min	47 (6.7)	141 (12.0)	130 (23.7)	0.001
Diabetes mellitus	398 (56.9)	627 (53.2)	275 (50.2)	0.02
Prior MI	84 (12.0)	114 (9.7)	65 (11.9)	0.60
Prior PCI	197 (28.2)	284 (24.1)	108 (19.7)	0.002
Medications prior to admission				
Aspirin	455 (65.1)	764 (65.0)	349 (63.7)	0.85
Clopidogrel	144 (20.6)	248 (21.1)	140 (25.5)	0.07
Beta blockers	334 (47.8)	558 (47.4)	258 (47.1)	0.97
RAASB	309 (44.2)	477 (40.5)	201 (36.7)	0.03
Statins	372 (53.2)	614 (52.1)	280 (51.1)	0.77
ST-segment deviation	340 (48.6)	565 (48.0)	276 (50.4)	0.32
Elevated levels of cardiac enzymes	262 (37.5)	482 (40.9)	226 (41.2)	0.28
LVEF of <45%	78 (11.2)	153 (13.0)	71 (13.0)	0.47
Heart failure	70 (10.0)	140 (11.9)	59 (10.8)	0.48

Data are presented as mean ± standard deviation or n (%).
BMI: body mass index; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; RAASB: renin angiotensin-aldosterone system blockers.

of patients are presented in Table 1. Obese patients tended to be younger (although not significantly so) and were more likely to be female ($P < 0.001$); to have hypertension ($P < 0.001$), diabetes mellitus ($P = 0.02$), hypercholesterolemia ($P < 0.001$), a family history of premature cardiovascular disease ($P = 0.004$), and a history of PCI ($P = 0.002$); and to use renin angiotensin-aldosterone system blockers compared with the other two groups. Obese patients were less likely to be smokers or have renal impairment. There were no significant differences in age, the rate of ST-segment deviation on electrocardiography, elevated blood levels of cardiac biomarkers, heart failure or a low left ventricular ejection fraction, prior myocardial infarction, chronic renal disease, and the use of drugs other than renin angiotensin-aldosterone system blockers among the three groups.

As indicated in Table 2, similar proportions of patients in the three groups underwent PCI for STEMI, NSTEACS, or stable coronary disease. The severity of coronary artery disease and the rate of PCI for multi-vessel disease were also not different among the three groups. The rate of periprocedural complications in obese patients during the index hospitalization was not different from that in the two other groups, and the length of hospital stay was also similar among the three groups. Obese patients were less likely to have a high Global

Table 2. Indications for PCI, details of coronary angiography and PCI, CAD characteristics, and in-hospital complications in three groups of patients stratified by BMI.

Clinical feature	BMI $\geq$30 kg/m^2 n = 699	BMI 25.0–29.9 kg/m^2 n = 1178	BMI <25 kg/m^2 n = 548	P
PCI indication				0.62
STEMI	195 (27.9)	360 (30.6)	170 (31.0)	
NSTEACS	343 (49.1)	540 (45.8)	249 (45.4)	
Stable coronary syndrome	161 (23.0)	278 (23.6)	129 (23.5)	
In-hospital medications				
Aspirin	690 (98.7)	1164 (98.8)	542 (98.9)	0.45
Second oral antiplatelet	684 (97.9)	1157 (98.2)	545 (99.5)	0.06
Thrombolysis	20 (2.9)	39 (3.3)	22 (4.0)	0.52
GPI	92 (13.2)	162 (13.8)	73 (13.3)	0.92
Beta blockers	550 (78.7)	937 (79.5)	436 (79.6)	0.78
RAASB	457 (65.4)	723 (61.4)	322 (58.8)	0.06
Statins	680 (97.3)	1148 (97.5)	529 (96.5)	0.49
GRACE risk score				
On admission	111.4 ± 34.1	115.4 ± 35.7	119.8 ± 36.8	0.001
Pre-discharge	71.9 ± 22.1	73.3 ± 22.6	76.0 ± 24.5	0.007
CRUSADE bleeding risk score	20.5 ± 13.8	21.9 ± 13.4	25.7 ± 13.9	<0.001
Coronary artery disease				0.41
One vessel	419 (59.9)	690 (58.6)	308 (56.4)	
Multi-vessel	280 (40.1)	489 (41.5)	240 (43.8)	
PCI				0.62
One vessel	510 (73.0)	850 (72.2)	380 (69.3)	
Multi-vessel	180 (25.7)	316 (26.8)	162 (29.6)	
LMCA	9 (1.3)	12 (1.0)	6 (1.1)	
In-hospital complications				
Ventricular tachyarrhythmia	1 (0.1)	11 (0.9)	3 (0.5)	0.08
Heart failure	51 (7.3)	98 (8.3)	45 (8.2)	0.72
Cardiogenic shock	4 (0.6)	10 (0.8)	0 (0.0)	0.10
Emergency CABG	1 (0.1)	1 (0.1)	1 (0.2)	0.85
Vascular access hematoma	21 (3.0)	28 (2.4)	17 (3.1)	0.62
Length of stay				0.96
$\leq$1 day	216 (30.9)	361 (30.6)	170 (31.0)	
2–3 days	420 (60.1)	709 (60.2)	334 (60.9)	
>3 days	63 (9.0)	108 (9.2)	44 (8.1)	

Data are presented as mean ± standard deviation or n (%).

CAD: coronary artery disease; BMI: body mass index; CABG: coronary artery bypass graft; CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; CVD: cardiovascular disease; GPI: glycoprotein IIb/IIIa inhibitors; GRACE: Global Registry of Acute Coronary Events; LMCA: left main coronary artery; NSTEACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; RAASB: renin angiotensin-aldosterone blockers; STEMI: ST-segment elevation myocardial infarction.

Registry of Acute Coronary Events risk score both on admission and before discharge. Moreover, the CRUSADE bleeding risk score was significantly different among the three groups ($P < 0.001$).

Different types of stents were used in this contemporary PCI registry, including second-generation drug-eluting stents, bare metal stents, and bioabsorbable scaffolds. However, the types of stents used were not different among the three groups of patients. At 1 year, aspirin and a second oral antiplatelet agent were used at similar rates among the three BMI groups. Furthermore, similar proportions of patients in the three groups were prescribed statins, beta blockers, renin-angiotensin blockers, glycoprotein inhibitors, and thrombolysis agents.

Association between BMI and major cardiovascular adverse events

The chi-square test revealed no significant association between BMI and stent thrombosis during the index hospitalization (X^2 $(2) = 1.30$), in which obese patients had an incidence rate of stent thrombosis similar to that in the other two groups. Moreover, a non-significant association was present between BMI and stent thrombosis at 1 month and 1 year after hospital discharge (X^2 $(2) = 1.40$ and 1.60, respectively). The incidence rates of cardiac mortality and major bleeding during the hospital stay at 1 month and 1 year were not significantly different among the three groups (Table 3). Moreover, the readmission rates for three major adverse events (ACS, heart failure, and coronary revascularization) were not different between the obese group and the other two groups of patients.

Discussion

The main findings of this contemporary Middle Eastern study of patients who underwent PCI were that obese and overweight patients accounted for 77% of all enrolled patients, obese patients had a higher prevalence of cardiovascular risk factors and comorbidities than non-obese patients, and obesity was not associated with a reduced incidence of periprocedural complications or major adverse cardiovascular events at 1 year compared with non-obesity after adjustment for potential confounders.

Table 3. Adverse cardiovascular events during hospitalization and at 1 month and 1 year of follow-up in three groups of patients stratified by BMI.

Event	BMI $\geq$30 kg/m^2 n = 699	BMI 25.0–29.9 kg/m^2 n = 1178	BMI <25 kg/m^2 n = 548	P
Cardiac mortality				
In hospital	4 (0.57)	12 (1.02)	3 (0.55)	0.44
At 1 month	6 (0.86)	18 (1.54)	5 (0.92)	0.34
At 1 year	10 (1.44)	27 (2.33)	11 (2.05)	0.31
Stent thrombosis				
In hospital	6 (0.86)	3 (0.25)	0 (0.00)	0.31
At 1 month	13 (2.73)	15 (1.29)	3 (0.55)	0.11
At 1 year	18 (3.46)	22 (1.91)	5 (0.91)	0.21
Major bleeding events				
In hospital	8 (1.14)	10 (0.85)	5 (0.91)	0.81
At 1 month	9 (1.28)	11 (0.94)	7 (1.28)	0.73
At 1 year	10 (1.43)	13 (1.12)	7 (1.28)	0.84
Readmission at 1 year				
ACS	43 (6.29)	55 (4.80)	26 (4.84)	0.34
Heart failure	8 (1.31)	13 (1.13)	7 (1.30)	0.93
Coronary revascularization	24 (3.50)	34 (2.97)	15 (2.79)	0.74

Data are presented as n (%).
ACS: acute coronary syndrome; BMI: body mass index

Obesity has become a global medical and socioeconomic burden of epidemic proportions and continues to substantially contribute to the development of numerous chronic metabolic and cardiovascular diseases.[2,13,14] The excess risk is mainly attributed to the presence of excess adipose tissue, which is capable of releasing several cytokines and bioactive mediators that play important roles in the pathogenesis of obesity-related disorders.[15,16]

Obesity is also associated with insulin resistance, hyperinsulinemia, hypertension, elevated levels of low-density lipoprotein cholesterol, low levels of high-density lipoprotein cholesterol, and hypertriglyceridemia.[2] Obesity may lead to hypertension by increasing activation of the sympathetic nervous system and angiotensin–aldosterone system.[2,7] The prevalence of diabetes mellitus is higher among obese than non-obese patients, a finding that is similar between the present study and other reports.[17,18] Obesity is considered a main predictor of insulin resistance that is correlated with increasing BMI and visceral fat, thus explaining the high prevalence of obesity among patients with diabetes.[17,18]

In contrast, the prevalence of renal impairment was significantly higher among patients with low/normal weight than among those who were overweight and obese. This result is consistent with the findings of a study conducting by Jongha,[19] who reported a higher prevalence of chronic kidney disease, end-stage renal disease, and worse survival among patients with a low BMI. However, another study indicated that there was no significant effect of obesity on renal function.[20]

In regard to the adverse negative impact of obesity on the cardiovascular burden, a few studies have described paradoxically longer survival among overweight and obese adults with and without chronic diseases.[16,21] The term "obesity paradox" was first described in 1999 in overweight and obese people undergoing hemodialysis[22] and later in patients with heart failure,[23] hypertension, ACS,[24] diabetes mellitus,[25] peripheral arterial disease,[26] and stroke.[27]

Explanations of the obesity paradox are not fully clear. Adipose tissue is not only a source of harmful mediators; it is also a major endocrine organ that produces anti-inflammatory agents including soluble products that neutralize the deleterious effects of tumor necrosis factor-alpha on the myocardium. Moreover, it is capable of storing lipophilic noxious substances that are potentially toxic to the body.[28,29]

An association of the obesity paradox with PCI was reported in two studies.[30] Both concluded that patients with a BMI of 27.5 to 30 kg/m^2 had a reduced risk of death during a 5- and 7-year follow-up. The performance of coronary interventions in obese patients has steadily increased during the last few decades[31] and has been shown to be associated with fewer repeated revascularizations in obese patients than non-obese patients, possibly due to a larger external elastic membrane that preserves the lumen dimensions, larger stent area, and presence of beneficial vasoactive properties that may offset the adverse effects of excess adipose tissue.[32] In the current study, we were unable to demonstrate the existence of the obesity paradox in our PCI population. Periprocedural complications during the hospital stay, the length of hospitalization, and the incidence of major adverse cardiovascular events at 1 year were not different between the obese group and the other two groups.

Our finding of the absence of the obesity paradox in patients undergoing PCI is consistent with the findings of other studies.[33,34] One possible explanation for the absence of the obesity paradox is the inherent weakness of the BMI to adequately evaluate the severity of obesity based on its inability to identify body weight components such as fat mass, fat-free mass, and lean mass.[35]

Critics of the obesity paradox have argued that this phenomenon is a product of methodological artifacts and inadequate control of confounding factors. Some have suggested that obese patients are provided a level of medical care better than that provided to others, thus mitigating the potential adverse influence of obesity.[36] Furthermore, some have raised concerns about the presence of reverse causation in obese patients, which refers to illness-induced weight loss. Obese patients with chronic illnesses could be healthier in the early stages of the disease, and as the illness advances they develop unintentional weight loss, which is an extremely significant predictor of mortality.[37,38] Moreover, the reviewed literature indicate that higher mortality rates among the patients in the low BMI categories could be attributed to sarcopenic obesity; i.e., low muscle mass in association with obesity. This condition exacerbates insulin resistance and dysglycemia and is associated with frailty and higher mortality rates.[39,40]

Regardless of whether the obesity paradox exists, obese patients with cardiovascular disease should continue to be encouraged to lose weight.[41] The safety and potential long-term benefits of purposeful weight loss in overweight and obese patients with coronary heart disease should be stressed.[42]

Limitations and recommendations

A few limitations in our study warrant discussion. Selection bias, collection of non-randomized data, and missing or incomplete information are inherent problems associated with observational registry studies. Participation was voluntary and enrollment of consecutive patients was encouraged, but this was not verified. Patients who were admitted with ACS and died before or shortly after admission were not represented in this study. The participating hospitals are high-volume tertiary care centers, and the results may not represent PCI practice and outcomes in the whole region. Our study only included patients who underwent PCI, so it cannot be generalized to patients with ACS who were treated conservatively or underwent coronary artery bypass graft surgery. We did not evaluate outcomes in patients with a BMI of <20 or >35 kg/m^2 separately because of the small numbers of patients in these groups (1.3% and 7.7%, respectively). We measured the BMI to define excess weight and obesity. Additionally, the BMI is a crude and flawed anthropometric biomarker that lacks the discriminating power to differentiate between lean body mass and fat mass. Although it is easy to calculate, it has problematic cut-off points, and some researchers advocate correlating events with measuring the visceral adipose tissue.[39] We did not correlate survival with the BMI changes during the 1-year follow-up that could have taken place due to patients' compliance with weight reduction advice. Weight fluctuations cannot be captured with a single BMI measurement. However, some longitudinal studies have relied on a single measure of BMI, similar to our methodology.[43] Future prospective studies will be conducted using different measures for obesity such as the waist–hip ratio, fat mass, fat-free mass, and lean mass.

Conclusions

Obesity is associated with several medical adverse events and multiple cardiac-related risk factors, and it is recognized as an independent risk factor for cardiovascular comorbidities.[40] In the current study, however, the incidence rates of major adverse cardiovascular events were the same in obese patients as in overweight and normal/underweight patients during the hospital stay and at 1 month and at 1 year after discharge. These findings indicate that the BMI is a weak risk factor for cardiovascular comorbidities in Arab Jordanian patients.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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