J Cardiol 2007 Aug; 50(2): 93－100

Obesity Not Associated With Medium-Term Prognosis Among Japanese Male Survivors Hospitalized for Acute Myocardial Infarction

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Abstract

Background. Obesity is an established risk factor for coronary heart disease. However, data on the relationship between obesity and prognosis following acute myocardial infarction (AMI) are still lacking in Japan.

Methods and Results. In the present study, 1,458 AMI patients were enrolled in the AMI-Kyoto Multi-Center Risk Study between January 2000 and December 2003. Among survivors of hospitalized AMI, clinical characteristics and medium-term prognosis were retrospectively compared between 240 normal weight male patients [body mass index (BMI) 18.5－25.0 kg/m^2, normal weight group], and 116 obese male patients (BMI $\geq$ 25.0 kg/m^2, obese group), who could be followed up after hospital discharge. The obese group were younger and had higher prevalence of smoking and hypercholesterolemia than the normal weight group. The two groups had similar angiographic findings and outcomes of primary percutaneous coronary intervention. During the follow-up period (mean 2.18 years for normal weight, 2.15 years for obese), overall mortality rate as well as event-free survival rate did not differ significantly between the two groups. Multivariate analysis showed the presence of previous myocardial infarction, diabetes mellitus, and age were predictors of medium-term mortality, but BMI was not.

Conclusions. These results suggest that obesity is not associated with increased medium-term mortality and cardiac morbidity in Japanese male survivors hospitalized for AMI.

J Cardiol 2007 Aug; 50(2): 93－100

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Manuscript received March 5, 2007; revised May 18, 2007; accepted May 25, 2007

Key Words
■Myocardial infarction, pathophysiology ■Obesity ■Prognosis

INTRODUCTION

Obesity is an independent risk factor for coronary heart disease (CHD)[1,2] and is increasing in prevalence because of diets high in fat and calories and a sedentary lifestyle with physical inactivity.[3−5] Long-term follow-up studies have provided evidence that obesity is associated with increased rates of cardiovascular morbidity and mortality.[6,7] Moreover, recent reports have demonstrated that body mass index (BMI) is independently associated with coronary events in patients with established CHD.[8,9]

In contrast, several recent clinical studies have indicated that the prognosis is more favorable for obese patients than normal weight patients and underweight patients after acute myocardial infarction (AMI) as well as after percutaneous/surgical coronary revascularization, which is termed as "the obesity paradox".[10−15] However, data on the relationship between obesity and prognosis following AMI are still lacking in Japan. Recently we showed that obesity is an independent risk for AMI in young-aged and middle-aged males, but not in females in Japan.[16] Therefore, we focused on the relationship between obesity and clinical outcome in male patients following AMI.

The AMI-Kyoto Multi-Center Risk Study, a large multicenter observational study in which 16 collaborating hospitals in Kyoto Prefecture have collected demographic, procedural, and outcome data on AMI patients, was established in 2000 to analyze this data and establish an emergency-hospital network for heart diseases in Kyoto.[16,17]

The present study assessed the impact of obesity on intermediate-term outcomes in male AMI patients after hospital discharge, using data from the AMI-Kyoto Multi-Center Risk Study.

SUBJECTS AND METHODS

Patient population

The present study included 1,458 consecutive patients with a diagnosis of AMI, who were admitted to AMI-Kyoto Multi-Center Risk Study Group Hospitals within 1 week after the onset of AMI from January 2000 to December 2003. Of these, 1,231 patients survived and 227 suffered in-hospital death. Data on baseline BMI were available in 683 (males 511, females 172) of the 1,231 patients. Based on the definition of obesity from the Japanese Society for the Study of Obesity, the male patients were divided into three categories based on the admission BMI: underweight ($< 18.5\,kg/m^2$, $n = 18$), normal weight ($18.5-25.0\,kg/m^2$, $n = 336$), and obese ($\geq 25.0\,kg/m^2$, $n = 157$). We excluded underweight patients from the present analysis, because the number of underweight patients was too small compared with those of normal weight patients and obese patients. Follow-up data after discharge were obtained for 240 of the 336 normal weight male patients (71.4%) (normal weight group) and 116 of the 157 obese male patients (73.9%) (obese group). We retrospectively compared clinical background, coronary risk factors, angiographic findings, acute results of primary percutaneous coronary intervention (PCI), and medium-term prognosis between the normal weight group and the obese group. The diagnosis of AMI required the presence of 2 of the following 3 criteria: 1) characteristic clinical history, 2) serial changes on the electrocardiography suggesting infarction (Q-waves) or injury (ST-segment elevations), and 3) transient increase in cardiac enzymes to more than 2-fold the upper limit of the normal range.

Data collection

The patients' demographic information, cardiovascular history, and risk factors (*i.e.*, smoking, hypercholesterolemia, hypertension, and diabetes mellitus), were recorded. Height and weight were measured at the time of admission. The values of BMI were calculated as the body weight in kilograms divided by the height in meters squared. Hypercholesterolemia was defined as total cholesterol ≥ 220 mg/d*l* or the use of cholesterol-lowering agents by patient; hypertension was defined as systemic blood pressure $\geq 140/90$ mmHg or the use of antihypertensive treatment; diabetes mellitus was defined as fasting blood sugar ≥ 126 mg/d*l* or the use of specific treatment. After informed consent to participate in the AMI-Kyoto Multi-Center Risk Study was confirmed by each patient, all in-hospital data were transmitted to the center located at the

Table 1 Clinical characteristics of the study patients (obese vs normal weight groups)

	Normal weight group (n=240) 18.5≦BMI<25.0	Obese group (n=116) 25.0≦BMI	p value
Age (yr, mean±SD)	65.4±11.6	58.7±12.3	<0.01
Previous myocardial infarction	34 (14.2)	17 (14.7)	NS
Previous PCI/CABG	21 (8.8)	12 (10.3)	NS
Risk factors			
Smoking	118 (49.2)	81 (69.8)	<0.01
Hypercholesterolemia	82 (34.2)	54 (46.6)	<0.05
Hypertension	113 (47.1)	64 (55.2)	NS
Diabetes mellitus	69 (28.8)	36 (31.0)	NS
Killip's classification class 3/4	17 (7.1)	1 (0.9)	<0.05
BMI (kg/m^2, mean±SD)	22.3±1.7	27.3±2.0	<0.01

( ): %.
BMI=body mass index; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting.

Department of Cardiology and Vascular Regenerative Medicine in Kyoto Prefectural University School of Medicine for analysis. The study protocol was approved by the ethics committee of each hospital.

Emergency coronary angiography and reperfusion therapy

Emergency coronary angiography (CAG) was performed using the standard technique. The coronary flow in the infarct-related artery was graded according to the classification used in the Thrombolysis in Myocardial Infarction (TIMI) trial. Significant coronary artery stenosis was defined as at least a 75% reduction in the internal diameter of the right, left anterior descending, or left circumflex coronary arteries and their major branches, or a 50% reduction in the internal diameter of the left main trunk. Non-significant stenosis was defined as coronary arterial narrowing less than significant stenosis. Patients with either angiographically normal coronary arteries or non-significant stenosis were classified as having zero-vessel disease. After the culprit lesions were ascertained by CAG, PCI was subsequently performed. Successful reperfusion was defined as the establishment of TIMI grade 3 flow in the infarct-related artery on the final CAG.

Follow-up

Follow-up data were obtained from hospital records or by interviewing (directly or by telephone) patients, their families, or their personal physicians as of January 31, 2005. Major adverse cardiac events (MACE) were defined as death, recurrence of AMI, percutaneous or surgical revascularization, and hospitalization for acute coronary syndrome, heart failure, or arrhythmia. Each death was categorized as cardiac or noncardiac. The primary end-point of the study was all-cause mortality during the follow-up period.

Statistics

Data are expressed as mean ± SD. The normal weight and obese groups were compared using the chi-square test for discrete variables and unpaired Student's t-test for continuous variables according to standard statistical methods. Survival and event-free survival curves were displayed using the Kaplan-Meier method, and differences were compared using the log-rank test. Correlates of death during follow-up period were determined by Cox model analysis. In all analyses, significance was accepted at $p < 0.05$.

RESULTS

Patient characteristics and risk factors

The clinical characteristics and risk factors in the two groups are summarized in **Table 1**. The obese group were younger and had higher prevalence of smoking and hypercholesterolemia than the normal weight group. In contrast, the normal weight group had higher prevalence of Killip grade ≥ 3 at admission than the obese group.

Table 2 Angiographic findings of the study patients

	Normal weight group (*n*=240) 18.5≦BMI<25.0	Obese group (*n*=116) 25.0≦BMI	*p* value
Emergent coronary angiography	220 (91.7)	108 (93.1)	NS
Culprit lesions			NS
Not definite	1 (0.5)	2 (0.9)	
Right coronary artery	78 (35.5)	45 (41.7)	
Left anterior descending coronary artery	107 (48.6)	46 (42.6)	
Left circumflex coronary artery	28 (12.7)	14 (13.0)	
Left main artery trunk	1 (0.5)	0	
Multivessels	5 (2.3)	1 (0.9)	
Number of diseased vessels			NS
0	0	0	
1	121 (55.0)	73 (67.6)	
2	71 (32.3)	28 (25.9)	
3	25 (11.4)	7 (6.5)	
Left main artery trunk	3 (1.4)	0	

( ) : %.

Table 3 Results of coronary intervention in the study patients

	Normal weight group (*n*=240) 18.5≦BMI<25.0	Obese group (*n*=116) 25.0≦BMI	*p* value
Primary percutaneous coronary intervention	208 (86.7)	102 (87.9)	NS
Pre TIMI grade			NS
0	112 (53.8)	62 (60.8)	
1	46 (22.1)	18 (17.66)	
2	20 (9.6)	13 (12.7)	
3	30 (14.4)	9 (8.8)	
Post TIMI grade			NS
0	2 (1.0)	4 (3.9)	
1	1 (0.5)	1 (1.0)	
2	10 (4.8)	3 (2.9)	
3	195 (93.8)	94 (92.2)	
Stent	165 (79.3)	84 (82.4)	NS
Coronary artery bypass grafting	2 (0.8)	1 (0.9)	NS

( ) : %.
TIMI=Thrombolysis in Myocardial Infarction. Other abbreviation as in Table 1.

Angiographic data

Table 2 shows the emergency coronary angiographic data in the two groups. The distributions of culprit lesions as well as number of diseased vessels did not differ between the two groups.

Results of percutaneous coronary intervention

Table 3 shows the results of PCI in the two groups. The distributions of TIMI grade before and after primary PCI did not differ significantly between the two groups. The acquisition rates of successful reperfusion and the rates of stent usage did not differ significantly between the two groups.

Prognosis

The median follow-up time was 2.18 years for

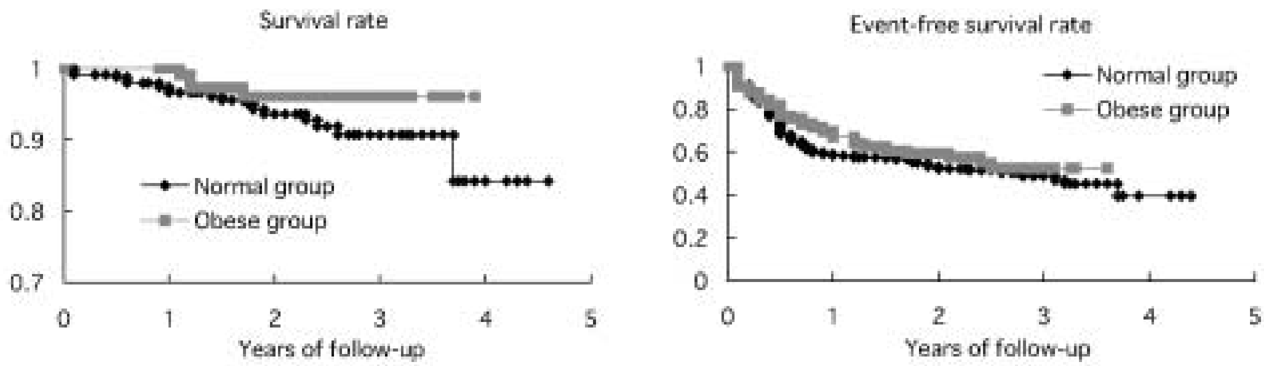

Fig. 1 Survival curve (*left*; $p = 0.184$) and event-free survival curve (*right*; $p = 0.319$) of the obese group vs the normal weight group

Table 4 Major adverse cardiac events among the study patients

	Normal weight group ($n = 240$) 18.5≤BMI<25.0	Obese group ($n = 116$) 25.0≤BMI	*p* value
Follow-up (yr, mean±SD)	2.18±0.90	2.15±0.77	NS
Event-free survival	124 (51.7)	67 (57.8)	NS
Death	17 (7.1)	4 (3.4)	NS
Cardiac-related	5	3	NS
Noncardiac-related	12	1	NS
Reinfarction	6 (2.5)	5 (4.3)	NS
Admission due to angina	35 (14.6)	15 (12.9)	NS
Admission due to CHF	14 (5.8)	4 (3.4)	NS
Percutaneous coronary intervention	86 (35.8)	38 (32.8)	NS
Coronary artery bypass grafting	19 (7.9)	4 (3.4)	NS

( ): %.
CHF = congestive heart failure. Other abbreviation as in Table 1.

the normal weight group and 2.15 years for the obese group. The medium-term prognosis did not differ significantly between the two groups (**Fig. 1**). The obese group had a 96.1% survival rate at 3.9 years compared with an 84.2% survival rate in the normal weight group ($p = 0.184$; **Fig. 1—left**). The obese group had a 52.6% event-free survival rate at 3.6 years compared with a 45.2% event-free survival rate in the normal weight group ($p = 0.319$; **Fig. 1—right**). **Table 4** lists MACE between the normal weight group and the obese group during the entire follow-up period. There were no significant differences in prevalence of any type of MACE between the two groups. During the follow-up period, there were 17 deaths in the normal weight group and 4 deaths in the obese group. The 17 deaths in the normal weight group consisted of 5 cardiac-related deaths (sudden death 2, AMI 1, heart failure 1, aortic dissection 1) and 12 noncardiac-related deaths (cancer 6, pneumonia 4, unknown 2). The 4 deaths in the obese group consisted of 3 cardiac-related deaths (AMI 2, malignant arrhythmia 1) and 1 noncardiac-related death (cerebral hemorrhage 1). Cardiac-related deaths accounted for most deaths in the obese group. In contrast, noncardiac-related death tended to be more frequent in the normal weight group compared with the obese group ($p = 0.051$). In order to assess the contribution of BMI, and other risk factors, a Cox proportional hazard model was developed for overall death (**Table 5**). The predictor of the medium-term mortality after hospitalization was the presence of previous myocardiol infarction [hazard ratio (HR) 4.146; 95% confidence interval (CI) 1.591−10.801, $p = 0.0036$], diabetes mellitus (HR 2.631; 95% CI 1.034−6.693, $p = 0.0423$),

Table 5 Mortality predictors in the study patients (Cox proportional hazard multivariate analysis)

	Relative risk (95% CI)	*p* value
BMI	0.915 (0.759−1.102)	0.3497
Age	1.083 (1.030−1.138)	0.0017
Previous myocardial infarction	4.146 (1.591−10.801)	0.0036
Killip's classification class	2.660 (0.849−8.331)	0.0931
Smoking	1.614 (0.638−4.079)	0.3118
Hypercholesterolemia	1.385 (0.557−3.443)	0.4839
Hypertension	0.792 (0.324−1.934)	0.6087
Diabetes mellitus	2.631 (10.34−6.693)	0.0423

CI = confidence interval. Other abbreviation as in Table 1.

and age (HR 1.083; 95% CI 1.030−1.138, $p = 0.0017$). In contrast, BMI was not an independent predictor of medium-term mortality in male patients following hospitalized AMI.

DISCUSSION

The major findings of the present multicenter study are that obesity is not associated with increased medium-term mortality and cardiac morbidity in male survivors of hospitalized AMI; and the presence of previous myocardial infarction, diabetes mellitus, and age were the independent predictors of the mid-term mortality, but BMI was not.

This study is the first to investigate the impact of obesity on medium-term prognosis in male patients following hospitalized AMI in Japan. The working hypothesis was that obese male patients have a worse medium-term outcome after hospitalized AMI compared with normal weight male patients. Contrary to our supposition, we found that the obese male patients and the normal weight male patients had similar mortality and cardiac morbidity during the mid-term follow-up period after hospitalized AMI, although the normal weight male patients tended slightly but not significantly to have higher mid-term mortality rate than obese male patients. In the present study, the majority of deaths during follow-up period in the normal weight male patients with AMI were attributed to noncardiac causes and most of the noncardiac deaths in the normal weight group were ascribed to cancer and pneumonia. Previous studies have also shown that underweight patients had poor prognosis and that the high mortality rate in this group was attributed to noncardiovascular causes, such as cancer, respiratory diseases, and other occult underlying disease.[6, 18] On the other hand, most deaths in the obese male patients with AMI were ascribed to cardiac causes including AMI in the present study.

Recent overwhelming evidence has indicated that adverse effects of obesity, such as a variety of metabolic disorders, cardiovascular morbidity, and mortality, are more tightly associated with central obesity than peripheral obesity.[19−21] Males are more prone to accumulate a central (visceral) pattern of fat distribution than females.[22] Indeed, previous studies including ours have shown that the susceptibility to the CHD risk of obesity is higher in males than in females.[6,16] Therefore, we focused on the effect of obesity on prognosis particularly in male patients with AMI, stratified by sex.

No significant difference in the prognosis between the obese AMI patients and the normal weight AMI patients in the present study might be partly due to the follow-up period being relatively short (mean 2.2 years) as well as the younger age (approximately 7 years) of the obese AMI patients. Previous studies have indicated that higher BMI was associated with an increased risk of reinfarction or cardiac death after first AMI during a 3-year follow-up period.[8, 23] The effects of obesity on cardiovascular morbidity and mortality increase with the duration of follow-up. The mortality in thin patients increases during the first years of follow-up, whereas that in obese patients increases during the subsequent follow-up period.[24−26] Another possible explanation is that fraction of the severely obese patients ($BMI \geq 30.0$ kg/m^2) in the obese group (12.1%), who have a higher risk of recurrent coronary events,[8] was relatively small in the present study. In addition, there is a possibility that BMI at hospital discharge might be lower than BMI at admission, because spontaneous weight reduction is common during hospitalization. This weight loss might contribute to the absence of significant difference in the mid-term outcomes between the obese and the normal weight AMI patients.

Study limitations

First, this is a retrospective analysis of a small number of patients. Second, BMI and follow-up data were not available for all patients. Third, we did not have adequate data for BMI at hospital discharge as well as medication prescribed at hospital discharge. Fourth, we had missed data regarding triglyceride and high-density lipoprotein cholesterol concentrations, which are indispensable data for examining dyslipidemia in obese patients. Furthermore, we have not accounted for the fat distribution, which may be better at predicting risk of CHD than BMI. Long-term follow-up studies and further prospective studies are needed to ascertain the effect of obesity on prognosis in Japanese patients with AMI.

CONCLUSIONS

The present study provides evidence that obesity is not associated with increased intermediate-term mortality in male survivors of hospitalized AMI. However, the small sample size of our report is a major limitation and a larger study during a longer follow-up period should be performed to confirm our findings.

Appendix

The following institutions and principal investigators participated in the present study as the AMI-Kyoto Multi-Center Risk Study Group: Kyoto City Hospital: Matsubara K, Shima M, Kiyama M; Kyoto Kidugawa Hospital: Miyanaga H, Nakagawa T, Matsui H, Kawa T, Kunieda Y; Kyoto Second Red Cross Hospital: Fujita H, Tanaka T, Inoue K, Matsuo A; Social Insurance Kyoto Hospital: Yamada C, Oda Y; Rakuwakai Marutamachi Hospital: Kusuoka S, Katamura M; Ayabe Municipal Hospital: Shiga K, Kohno Y, Adachi Y; Kameoka Municipal Hospital: Kuriyama T, Matsuo R; Maizuru Medical Center: Harada Y, Hikosaka T, Nakagami T, Nakajima N; Kyoto Saiseikai Hospital: Yamahara Y, Ishibashi K, Kuroyanagi A; Gakkentoshi Hospital: Sakai R, Akashi K; Nantan General Hospital: Keira N, Nomura T; Kouseikai Takeda Hospital: Kinoshita N, Irie H, Nakamura R; Fukuchiyama Municipal Hospital: Nishio M, Sakamoto T, Hayashi H; Kyoto Prefectural Yosanoumi Hospital: Kimura S, Nishikawa S, Takeda M, Tateishi K; Kyoto First Red Cross Hospital: Miyagawa K, Torii S; Kyoto Prefectural University School of Medicine: Shirayama T, Tsutsumi Y, Takahashi T, Shiraishi H, Yamada T, Nishizawa S.

要　約

肥満は日本人男性の急性心筋梗塞症例において退院後の中間期予後に影響を及ぼさない

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京都心筋梗塞研究会

背景と目的: 肥満は冠動脈疾患の独立した危険因子の一つである．一方，我が国では肥満と急性心筋梗塞症例の予後との関連について検討されていない．そこで今回，日本人男性の急性心筋梗塞症例において肥満が退院後の中間期予後に及ぼす影響について検討した．

方法と結果: 2000年1月−2003年12月に京都心筋梗塞研究会に登録された急性心筋梗塞1,458例をもとにして，退院後の予後が確認できた男性症例を体格指数(BMI)が25.0(kg/m^2)以上の肥満群116例と18.5以上25.0未満の正常体重群240例を対象に，臨床背景，血管造影所見，経皮的冠動脈形成術の結果および退院後の中間期予後について検討した．平均観察期間は肥満群で2.15年，正常体重群で2.18年であった．肥満群は正常体重群より若齢で，喫煙，高脂血症を有する頻度が有意に高値であったが，入院時のKillipグレードが3以上の占める割合は低値であった．中間期の生存率および心イベントフリーの生存率については両群間に有意差は認められなかった．多変量解析では，陳旧性心筋梗塞，糖尿病，年齢が独立した中間期の予後規定因子であったが，BMIは予後規定因子ではなかった．

結　論: 日本人男性の急性心筋梗塞症例において，肥満は退院後の中間期予後に影響を及ぼさなかった．

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