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Pathogenesis of Acute Myocardial Infarction in Young Male Adults With or Without Obesity

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Abstract

Objectives. Obesity may be linked with coronary atherosclerosis in young males. This study investigated the etiology of acute myocardial infarction (AMI) in young Japanese male patients with or without obesity.

Methods and Results. This retrospective study included 2,230 AMI patients enrolled in the AMI-Kyoto Multi-Center Risk Study between January 2000 and December 2005. Clinical background, risk factors, angiographic findings, acute results of primary percutaneous coronary intervention (PCI), and in-hospital outcome were evaluated in 33 young male patients < 40 years old. The study group was divided into the obese group [body mass index (BMI) ≥ 25, $n = 21$] and non-obese group (BMI < 25, $n = 12$). Four of the 12 non-obese patients had underlying disease (Kawasaki disease 2, Buerger's disease 1, drug abuse 1). The non-obese group had a higher prevalence of underlying disease than the obese group. The non-obese group had a higher incidence of left anterior descending coronary artery as culprit lesion and higher Thrombolysis in Myocardial Infarction (TIMI) grade flow in the infarct-related artery before primary PCI. The acquisition rates of TIMI 3 flow after primary PCI and in-hospital outcome did not differ between the two groups.

Conclusions. Non-obese young AMI male patients have a higher frequency of underlying disease. Most young male AMI patients were obese, suggesting that obesity may be important in the pathogenesis of AMI in young male adults.

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Key Words
■Myocardial infarction, pathophysiology ■Obesity ■Kawasaki disease

INTRODUCTION

Young adults are a relatively small portion of patients with acute myocardial infarction (AMI), but are an important group to examine for the purpose of risk factor modification and secondary prevention. Young AMI patients are characterized by a relatively high incidence of normal coronary arteries, non-obstructive stenosis, or single-vessel disease, and high prevalence of current smoking, hyperlipidemia, and family history.[1–6] In addition, the etiology of AMI in young patients may involve non-traditional coronary risk factors such as vasospastic tendencies, thrombophilic conditions, vasculitis, past history of Kawasaki disease (KD), and drug abuse.[7–12] However, the pathophysiology of young Japanese AMI patients has not been fully investigated.

Obesity is a risk factor for coronary heart disease (CHD) among adults[13] and is increasing in prevalence among young adults as well as adults.[14,15] Obesity had a significant association with coronary atherosclerosis in young male adults, particularly in those with the central pattern of adiposity, whereas the association of obesity with coronary atherosclerosis is low in young female adults.[16] Adiposity and its metabolic disturbances (metabolic syndrome) are also associated with early atherosclerotic change in adolescents.[17] Young AMI patients have greater body mass index (BMI) than non-young AMI patients.[18] Therefore, obesity may be one of the risk factors in young male patients with AMI.

The present study evaluated the etiology of AMI in young Japanese male patients with or without obesity using data from the AMI-Kyoto Multi-Center Risk Study.

SUBJECTS AND METHODS

Patient population

The present study analyzed the records of 2,230 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 2005. Thirty four patients $<$ 40 years of age at the time of infarction were identified. All these patients were males, except for one female patient with missing data of BMI. Therefore, the study group (all male, $n = 33$) was divided into the obese group (BMI ≥ 25, $n = 21$) and the non-obese group (BMI < 25, $n = 12$). The clinical characteristics and in-hospital outcome were assessed in these groups. The diagnosis of AMI required the presence of 2 of the following 3 criteria: characteristic clinical history, serial changes on the electrocardiogram (ECG) suggesting infarction (Q-waves) or injury (ST-segment elevations), and transient increase in cardiac enzymes to more than 2 times the upper limit of normal range.

Data collection

The patients' demographic information, cardiovascular history, risk factors (*i.e.*, smoking, hypercholesterolemia, hypertension, and diabetes mellitus), and family history 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 per meters squared. Hypercholesterolemia was defined as total cholesterol $\geq$ 220 mg/d*l* or the use of cholesterol-lowering agents; 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 $\geq$ 126 mg/d*l* or the use of specific treatment. Family history of CHD in siblings, parents, parents' siblings, or grandparents was registered. All patients gave informed consent to participate in the AMI-Kyoto Multi-Center Risk Study. All in-hospital data were transmitted to the center located at the Department of Cardiology and Vascular Regenerative Medicine in Kyoto Prefectural University of Medicine Graduate School of Medical Sciences for analysis. The study protocol was approved by the ethics committee of all hospitals.

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 but 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, percutaneous coronary intervention (PCI) was performed. Successful reperfusion was defined as the establishment of TIMI grade 3 flow in the infarct-related artery on the final CAG. Left ventriculography was performed at the time of either initial CAG or follow-up CAG before discharge.

Statistics

Data are expressed as mean $\pm$ SD. The obese and non-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. Significance was accepted at $p < 0.05$.

RESULTS

Patient characteristics

The clinical characteristics of all young AMI patients are summarized and listed in order of BMI in **Table 1**. Approximately two thirds of the young male adults with AMI were obese (BMI $\geq$ 25). Four of the 12 non-obese young AMI patients had an obvious underlying disease (KD 2, Buerger's disease 1, drug abuse 1). Although Patient 1 had no apparent history of KD, the wall structure of the regressed coronary aneurysm in the culprit lesion on intravascular ultrasound imaging (IVUS) closely resembled that associated with KD, suggesting the presence of underlying atypical KD. Patient 2 was identified as having Buerger's disease 6 months before the onset of AMI. Patient 4 had taken overdoses of anti-common cold drugs containing ephedrine and caffeine in the 10 years before the onset of AMI. Patient 6 had a history of KD at 3 years of age. Repeat CAG and IVUS showed a neo-coronary aneurysm in the culprit lesion.

Risk factors

The clinical characteristics and the risk factors in the obese and non-obese groups are summarized in **Table 2**. The non-obese group had a higher prevalence of underlying disease than the obese group. Prevalence of risk factors did not differ between the two groups. Killip grade $\geq$ 3 at admission did not differ between the two groups.

Angiographic data

Table 3 shows the emergency coronary angiographic data in the obese group and the non-obese group. Emergency CAG was performed in 12 of the non-obese group (100%) and 20 of the obese group (95.2%). The non-obese group had a higher frequency of culprit lesion in the left anterior descending coronary arteries and a lower frequency in the right coronary arteries. Number of diseased vessels did not vary between the two groups.

Results of coronary intervention

Table 4 shows the results of PCI in the obese and non-obese groups. PCI was performed in 12 of the non-obese group (100%) and 18 of the obese group (85.7%). The non-obese group had a higher TIMI grade flow in the infarct-related artery before primary PCI. The acquisition rates of successful reperfusion did not differ significantly between the two groups.

In-hospital outcome

Table 5 shows the in-hospital outcomes in the obese and non-obese groups. There was no significant difference in in-hospital survival rates between the obese group (95.2%) and the non-obese group (100%). There was one cardiac-related death in the obese group. The length of hospital stay in the non-obese group was significantly longer than that in the obese group, but maximal creatine phosphokinase level and ejection fraction of left ventricle did not differ between the two groups.

DISCUSSION

The major findings of the present multi-center study are as follows: most young male AMI patients were obese; and non-obese young male AMI patients tended to have a non-atherosclerotic etiology of AMI, a higher incidence of left anterior descending coronary artery as the culprit lesion, a higher TIMI grade flow in the infarct-related artery before primary PCI, and a longer length of hospital stay, compared with the obese.

The etiology of AMI in young adults is unclear. In the present study, one third of the non-obese young male AMI patients had obvious non-athero-

Table 1 Clinical characteristics of the young male patients with acute myocardial infarction

Patient No.	Age (yr), sex	Height (cm)	Weight (kg)	BMI (kg/m^2)	*No. of risk factors	Culprit lesion	Underlying disease
1	20, M	170	56	19.4	0	LAD	Atypical KD
2	24, M	172	58	19.6	1	LAD	Vasculitis
3	36, M	170	63	21.8	1	RCA	Not definite
4	27, M	175	70	22.9	1	LAD	Drug abuse
5	37, M	175	70	22.9	2	LAD	Not definite
6	26, M	170	69	23.9	1	LAD	KD
7	39, M	163	64	24.1	1	LAD	Not definite
8	36, M	173	72	24.1	0	LAD	Not definite
9	34, M	170	70	24.2	2	LAD	Not definite
10	35, M	170	70	24.2	1	RCA	Not definite
11	37, M	165	66	24.3	3	LAD	Not definite
12	33, M	165	67	24.6	2	LAD	Not definite
13	34, M	184	85	25.1	0	RCA	Not definite
14	37, M	170	73	25.3	2	RCA	Not definite
15	36, M	172	76	25.7	0	LCX	Not definite
16	38, M	168	74	26.2	3	LAD	Not definite
17	28, M	163	70	26.3	2	RCA	Not definite
18	39, M	171	77	26.4	1	Not definite	Not definite
19	38, M	175	82	26.8	2	LCX	Not definite
20	37, M	171	80	27.4	2	RCA	Not definite
21	36, M	180	90	27.8	1	LAD	Not definite
22	34, M	179	90	28.1	2	LAD	Not definite
23	27, M	178	89	28.1	0	None	Not definite
24	27, M	172	87	29.4	1	RCA	Not definite
25	34, M	174	90	29.7	4	RCA	Not definite
26	39, M	173	89	29.8	3	RCA	Not definite
27	35, M	168	85	30.1	0	LAD	Not definite
28	32, M	177	96	30.7	2	LAD	Not definite
29	26, M	170	89	30.8	2	RCA	Not definite
30	36, M	170	93	32.2	2	RCA	Not definite
31	38, M	165	88	32.4	2	RCA	Not definite
32	34, M	180	105	32.4	3	RCA	Not definite
33	35, M	162	85	32.4	2	RCA	Not definite

*Smoking, hypercholesterolemia, hypertension, and diabetes mellitus : Criteria described in Methods.
BMI＝body mass index ; M＝male ; LAD＝left anterior descending coronary artery ; RCA＝right coronary artery ; LCX＝left circumflex artery ; KD＝Kawasaki disease.

sclerotic causes, but coronary atherosclerosis might be the most common etiology of all young male AMI patients, particularly young AMI patients with obesity.[7,19] Approximately half of young female AMI patients (＜50 years) had non-atherosclerotic etiology of AMI, whereas only 1% of young male AMI patients had non-atherosclerotic disease.[12] Taken together, young male AMI patients might have a lower frequency of non-atherosclerotic underlying disease, compared with young female AMI patients. However, young male AMI patients without obesity might have a relatively high prevalence of non-atherosclerotic underlying disease.

AMI in young adults due to coronary artery vasculitis such as antecedent KD, collagen disease, Takayasu's aortitis, and Buerger's disease is extremely rare.[7,20,21] KD is an acute multisystem vasculitis of unknown etiology, predominantly

Table 2 Clinical characteristics of the young male acute myocardial infarction patients with or without obesity

	Non-obese group, BMI＜25 (n=12)	Obese group, BMI≥25 (n=21)	p value
Age (yr)	32.0±6.1	34.3±4.1	NS
Male	12(100)	21(100)	
BMI (kg/m^2)	23.0±1.8	28.7±2.5	＜0.01
Underlying disease	4(33.3)	0	＜0.01
Risk factors			
Smoking	8(66.7)	15(71.4)	NS
Hypercholesterolemia	6(50.0)	11(52.4)	NS
Hypertension	1(8.3)	5(23.8)	NS
Diabetes mellitus	0	5(23.8)	NS
Family history	2(16.7)	4(19.0)	NS
*No. of risk factors	1.25±0.87	1.71±1.10	NS
Killip's classification 3/4	1(8.3)	1(4.8)	NS

Continuous values are mean ±SD. ( ): %.
*Smoking, hypercholesterolemia, hypertension, and diabetes mellitus : Criteria described in Methods.
Abbreviation as in Table 1.

Table 3 Angiographic findings of the young male acute myocardial infarction patients with or without obesity

	Non-obese group, BMI＜25 (n=12)	Obese group, BMI≥25 (n=21)	p value
Emergent CAG	12(100)	20(95.2)	NS
Culprit lesions			
None	0	1(5.0)	＜0.05
RCA	2(16.7)	12(60.0)	
LAD	10(83.3)	5(25.0)	
LCX	0	2(10.0)	
No. of diseased vessels			
0	0	1(5.0)	NS
1	9(75.0)	17(85.0)	
2	3(25.0)	1(5.0)	
3	0	1(5.0)	

( ): %.
CAG＝coronary angiography. Other abbreviations an in Table 1.

occurring in infants and young children. Twenty-five percent of patients with acute KD have coronary aneurysms, and about 50% of patients with acute KD and coronary aneurysms showed regression of the aneurysms on follow-up angiography 1 or 2 years after onset.[22] The regressed aneurysms

Table 4 Results of coronary intervention in the young male acute myocardial infarction patients with or without obesity

	Non-obese group, BMI＜25 (n=12)	Obese group, BMI≥25 (n=21)	p value
Primary PCI	12(100)	18(85.7)	NS
Pre TIMI grade			
0	7(58.3)	12(66.7)	＜0.01
1	0	6(33.3)	
2	2(16.7)	0	
3	3(25.0)	0	
Post TIMI grade			
0	0	0	NS
1	0	0	
2	0	2(11.1)	
3	12(100)	16(88.9)	
Type of procedure			
Aspiration	1(8.3)	7(38.9)	NS
Stent	10(83.3)	15(83.3)	NS
IABP	3(25.0)	2(11.1)	NS
PCPS	0	1(5.6)	NS

( ): %.
PCI ＝ percutaneous coronary intervention ; TIMI ＝ Thrombolysis in Myocardial Infarction ; IABP＝intraaortic balloon pumping ; PCPS＝percutaneous cardiopulmonary support. Other abbreviation as in Table 1.

Table 5 In-hospital outcome

	Non-obese group, BMI＜25 (n=12)	Obese group, BMI≥25 (n=21)	p value
Length of hospital stay (day)	29.7±15.2	15.9±9.5	＜0.05
Max CPK (IU/l)	3,677.3±2,756.8	3,627.6±4,604.0	NS
LVEF (%)	55.8±9.4	61.0±9.6	NS
Acute occlusion	0	0	NS
SAT	1	0	NS
MR/VSP/rupture	0	0	NS
Death	0	1(4.8%)	NS

Continuous values are mean±SD.
Data on LVEF available only for 9 of the non-obese and 15 of the obese patients.
CPK＝creatine phosphokinase ; LVEF＝left ventricular ejection fraction ; SAT＝subacute stent thrombosis ; MR＝mitral regurgitation ; VSP＝ventricular septal perforation. Other abbreviation as in Table 1.

demonstrated marked thickening of the intima with or without calcification, similar to the early atherosclerotic changes in adults,[23] and CHD develops in approximately 5% of all patients during long-term follow-up.[22] On the other hand, drug abuse, such as cocaine, amphetamine, ephedrine, or caffeine, has been implicated as one of the triggers for coronary spasm leading to AMI.[11,24–26] Therefore, ephedrine and caffeine in anti-common cold drugs might have been very inportant in the pathogenesis of AMI in Patient 4.

In Japan, the prevalence of "obesity" defined by the World Health Organization (WHO) standard (BMI ≥ 30) is lower (3%), compared with those in Western countries (20% in UK, 23% in USA),[27] whereas the prevalence of "overweight" (30 > BMI ≥ 25) defined by the WHO Expert Committee is 20–25%. In addition, the WHO Expert Committee has indicated the unfavorable effect of overweight in association with enhanced mortality,[28] and the Japanese Society for the Study of Obesity redefined "obesity" as a BMI greater than or equal to 25.0.[29] Therefore, the present study employed the definition of obesity (BMI ≥ 25.0) of the Japanese Society for the Study of Obesity. However, BMI does not reflect body fat distribution, which might be a more crucial factor for morbidity.

The data regarding the association of obesity with atherosclerosis and CHD have been inconsistent for many years,[30,31] but recent accumulating findings have indicated that obesity is an independent CHD risk factor in adults.[13,32] Moreover, obesity has a significant relationship with coronary atherosclerosis in young male adults, particularly in those with central obesity, but little relationship in young female adults.[16] Obesity and its metabolic impairments (metabolic syndrome) are also associated with impaired endothelial function and early atherosclerotic change in adolescents.[17,33,34] Our recent report showed that young AMI patients have greater BMI than non-young AMI patients.[18] In the present study, two thirds of young male adults with AMI were obese and one third of non-obese patients had underlying disease. Therefore, obesity is probably very important in the pathogenesis of AMI in the majority of young male adults.

The precise mechanism by which obesity exaggerates atherosclerosis is not fully understood. The atherogenic effects of obesity are partly mediated through coexisting coronary risk factors.[35–37] Recently, the importance of adipose tissue has received more attention, particularly visceral fat tissue, for secreting proinflammatory cytokines and prothrombogenic factors in the development of atherosclerotic diseases and subsequent occurrence of CHD.[38–44] Although the present study had no data concerning visceral fat tissue, such as waist circumference and abdominal computed tomography, previous findings also support the current emphasis on control of obesity, particularly visceral obesity, to prevent CHD in young adults.

In the present study, the non-obese young male AMI patients tended to have a higher incidence of left anterior descending coronary artery as a culprit lesion, a higher TIMI grade flow in the infarct-related artery before primary PCI, and a longer length of hospital stay. We cannot explain why the non-obese young male AMI patients had those clinical characteristics. However, we cannot rule out the possibility that coronary obstruction in non-obese young males might be more thrombogenic, more spasmogenic, and less atherosclerotic, compared with that in obese young males, so pre-medication in the emergency room, such as heparin, antiplatelet drugs, and vasodilator, might obtain recanalization of the infarct-related coronary artery before primary PCI. The prolonged hospital stay in non-obese young male AMI patients might be due in part to the preponderance of anterior infarction.

Study limitations

First, this is a retrospective analysis of a very small number of patients. Second, the present study population consisted of AMI patients who were admitted to collaborating hospitals in Kyoto Prefecture, so might not reflect the entire Japanese population. Further prospective studies or controlled case studies are needed to ascertain the pathogenesis in young Japanese patients with AMI.

CONCLUSIONS

The present study provides evidence that, except for non-obese patients with underlying disease, most young male AMI patients were obese, suggesting that obesity should be corrected for primary prevention of AMI in young male adults. In addition, we should pay attention to the underlying disease in non-obese young male patients with AMI. However, the very small sample size of our report is a major limitation and a larger study should be performed to confirm our findings.

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Appendix

The following institutions and principal investigators participated in the present study as the AMI-Kyoto Multi-Center Risk Study Group: Kyoto Municipal Hospital: Furukawa K, Matsubara K, Ashida T; Kyoto Kidugawa Hospital: Miyanaga H, Nakagawa T, Matsui H; Kyoto Second Red Cross Hospital: Kitamura M, Inoue N, Fujita H, Tanaka T, Inoue K, Matsuo A, Suzuki K; Social Insurance Kyoto Hospital: Yamada C, Oda Y, Inoue M; Rakuwakai Marutamachi Hospital: Kusuoka S, Katamura M; Nantan General Hospital: Okada T; Ayabe Municipal Hospital: Shiga K, Kohno Y; Kameoka Municipal Hospital: Kuriyama T; Maizuru Medical Center: Harada Y, Yamanaka S; Kyoto Saiseikai Hospital: Yamahara Y, Ishibashi K, Kuroyanagi A; Gakkentoshi Hospital: Sakai R, Akashi K; Kouseikai Takeda Hospital: Ito K, Kinoshita N; Kyoto Prefectural Yosanoumi Hospital: Keira N, Kimura S; Fukuchiyama Municipal Hospital: Yamamoto K; Kyoto Prefectural University of Medicine Graduate School of Medical Sciences: Shirayama T, Tsutsumi Y, Takahashi T, Shiraishi H, Nakamura T.

要　　約

若年男性における急性心筋梗塞の成因について：肥満の側面からの検討

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目　的：近年，若年男性において冠動脈硬化と肥満との関連性が指摘されている．一方，日本では若年者の急性心筋梗塞の成因について十分に検討されていない．そこで今回，日本人男性の急性心筋梗塞の成因について，肥満の有無の側面から検討した．

方法と結果：2000年1月−2005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症例2,230例のうち，発症時40歳未満の男性症例の33例を対象とした．対象を体格指数（BMI）が25以上の肥満群21例と25未満の非肥満群12例とに分け，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院内予後について検討した．非肥満群12例のうち4例で基礎疾患を認め（川崎病2例，Buerger病1例，薬物乱用1例），肥満群と比較して基礎疾患を有する頻度が有意に高値であった．非肥満群では，左前下行枝を責任血管とする割合および経皮的冠動脈形成術前のTIMIグレードが肥満群と比較して有意に高値であった．経皮的冠動脈形成術後のTIMIグレードおよび院内予後に両群間で差を認めなかった．

結　論：肥満のない若年男性の急性心筋梗塞症例では基礎疾患が存在することがあるが，それらの症例を除くと大部分の症例で肥満を認め，若年男性の急性心筋梗塞の成因として肥満の関与が示唆された．

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