Relation of Obesity to Acute Myocardial Infarction in Japanese Patients

Differences in Gender and Age

Jun Shiraishi, MD; Yoshio Kohno, MD; Takahisa Sawada, MD; Shinya Nishizawa, MD; Masayas Arik, MD; Mitsuyoshi Hadase, MD; Masayuki Hyogo, MD; Takakzu Yagi, MD; Takatomo Shima, MD; Atsuko Nakazawa, MD; Masako Shigeta, MD; Hiroiuk Yamada, MD; Tetsuya Tatsumi, MD; Akhiro Azuma, MD; Hiroaki Matsubar, MD

on Behalf of the AMI-Kyoto Multi-Center Risk Study Group

Obesity is a risk factor for coronary heart disease (CHD) among adults1 and is increasing in prevalence among young adults, as well as adults. A recent report indicated a significant association of obesity with coronary atherosclerosis in young male adults, particularly in those with a central pattern of adiposity, and little association of obesity with coronary atherosclerosis in young female adults.4 Still another recent report points out that adiposity and its metabolic disturbances (ie, metabolic syndrome) are associated with early atherosclerotic change in adolescents.5 Recently we demonstrated that young Japanese patients with acute myocardial infarction (AMI) have a higher body mass index (BMI) than controls. In young males, as well as in middle-aged and older females, cases had a higher prevalence of smoking than controls. Except for very old males, the prevalences of hypercholesterolemia, hypertension, and diabetes mellitus were higher in each subgroup of cases than in controls. Multivariate logistic regression analysis revealed that obesity (BMI ≥25) was an independent risk factor for AMI in young and middle-aged males, but not in females, whereas smoking was an independent risk factor for AMI in middle-aged and older females as well as in older males.

Conclusions Obesity is significantly associated with AMI, independent of the classic coronary risk factors, in young and middle-aged males. These findings support the current emphasis on controlling obesity to prevent coronary events in young Japanese male adults. (Circ J 2006; 70: 1525 –1530)

Key Words: Acute myocardial infarction; Japan; Obesity; Risk factors; Smoking; Young adults

Methods

Case and Control Subjects

From January 2000 to June 2004, 1,651 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, were enrolled in the present study. 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 in order to analyze these data and establish an emergency-hospital network for heart diseases in Kyoto.6,7 The Kyoto Citizen’s Health and Nutrition Study was performed among residents in Kyoto Prefecture, in order to examine behavior and lifestyle habits and develop effective public health interventions.8,9 In the present study we used cases from the AMI-Kyoto Multi-Center Risk Study, and controls from the Kyoto Citizen’s Health and Nutrition Study, respectively, to assess obesity as a risk factor in subgroups of 20-year age bands of each gender separately, based on a multi-center case-control study.

Methods

Case and Control Subjects

From January 2000 to June 2004, 1,651 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, were enrolled in the present study.
study. Of these, 1,260 AMI patients for whom the data concerning clinical characteristics and risk factors were available, were assigned as the case subjects. The diagnosis of AMI required the presence of 2 of the following 3 criteria: (1) characteristic clinical history, (2) serial changes on the ECG suggesting infarction (Q-waves) or injury (ST-segment elevations), and (3) transient increase in cardiac enzymes to more than 2-fold the normal laboratory values.

Control subjects comprised residents in Kyoto Prefecture who were involved in the Kyoto Citizen’s Health and Nutrition Study as of November 1998. We enrolled 3,775 consecutive individuals aged more than 20 years who did not have a history of cardiovascular, renal, or cerebrovascular diseases.

Both the case and control subjects were classified into 20-year age bands. We retrospectively examined obesity and other risk factors between cases and controls in each subgroup of young-aged males (20–40 years), middle-aged males or females (40–60 years), older males or females (60–80 years), and very old males or females (80–100 years).

Data Collection

The demographic information and risk factors for the cases were recorded. Obesity was defined as a BMI ≥25 kg/m². Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl or the use of cholesterol-lowering agents; hypertension was defined as systemic blood pressure ≥140/90 mmHg or a history of previous treatment; diabetes mellitus was defined as fasting blood sugar ≥126 mg/dl or the use of specific treatment. After informed consent to participate in the AMI-Kyoto Multi-Center Risk Study was given by each patient, all the in-hospital data were transmitted to the collection center located at the Department of Cardiology and Vascular Regenerative Medicine in Kyoto Prefectural University School of Medicine for analysis. The study protocol was approved by each hospital’s ethics committee.

The personal characteristics, behavior, lifestyle habits, such as smoking status and alcohol consumption, and medical history of hypercholesterolemia, hypertension, diabetes mellitus, and other diseases of the controls were obtained from the questionnaires used in the Kyoto Citizen’s Health and Nutrition Study. The questionnaires were mailed to residents at random and then collected by investigators of each health center in Kyoto Prefecture.

Data on BMI were available in all 27 young, 202 of 276 middle-aged, 367 of 511 older, and 58 of 90 very old males, and in 17 of 29 middle-aged, 139 of 200 older, and 83 of 127 very old females.

### Table 1 Clinical Characteristics of the Cases and Controls by Gender and Age

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Young (20–40 years)</th>
<th>Middle-aged (40–60 years)</th>
<th>Older (60–80 years)</th>
<th>Very old (80–100 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>p value</td>
<td>Cases</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>27</td>
<td>495</td>
<td></td>
<td>276</td>
</tr>
<tr>
<td>Age (mean years ± SD)</td>
<td>33.2 ± 5.1</td>
<td>29.3 ± 5.8</td>
<td>&lt;0.001</td>
<td>53.4 ± 4.7</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>26.7 ± 3.7</td>
<td>22.2 ± 3.2</td>
<td>&lt;0.001</td>
<td>24.5 ± 3.1</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>20 (74.1)</td>
<td>225 (45.5)</td>
<td>&lt;0.001</td>
<td>179 (64.9)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>16 (59.3)</td>
<td>5 (1.0)</td>
<td>&lt;0.001</td>
<td>109 (39.5)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>6 (22.2)</td>
<td>4 (0.8)</td>
<td>&lt;0.001</td>
<td>119 (43.1)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>0</td>
<td>2 (0.4)</td>
<td>NS</td>
<td>75 (27.2)</td>
</tr>
</tbody>
</table>

### Data on BMI

Data on BMI were available in all 27 young, 202 of 276 middle-aged, 367 of 511 older, and 58 of 90 very old males, and in 17 of 29 middle-aged, 139 of 200 older, and 83 of 127 very old females.
Fig 2. Prevalence of obesity and smoking by gender and age groups. Open bar, cases; closed bar, controls. *p<0.01 vs controls. **p<0.05 vs controls.

Fig 3. Prevalence of hypercholesterolemia, hypertension, and diabetes mellitus by gender and age groups. Open bar, cases; closed bar, controls.
Statistical Analysis

Data are expressed as mean ± SD. The cases and controls were compared using the chi-square test for discrete variables and unpaired Student’s t-test for continuous variables according to standard statistical methods. The odds ratio and 95% confidence intervals assessing the risk of onset of AMI associated with obesity or smoking were estimated by multivariate logistic regression analysis of the case subjects having data on BMI and the control subjects. In all analyses, significance was accepted at p<0.05.

Results

Fig 1 shows the number of AMI cases, as stratified by gender and age. There were no young females among them. The clinical characteristics and risk factors of the cases and the controls, as stratified by gender and age, are shown in Table 1, and Figs 2 and 3. Irrespective of gender, the case group was significantly older than the control group, except for very old males. The case group had a significantly greater BMI and a higher prevalence of obesity than the control group for young, middle-aged, and older males, as well as for older females. The case group had a significantly higher prevalence of smoking than the control group in young males, as well as in middle-aged and older females. Except for very old males, the prevalences of hypercholesterolemia, hypertension, and diabetes mellitus were significantly higher in the case group than in the control group of each gender and age group.

As shown in Table 2, obesity was a significant risk for AMI in young and middle-aged males, after adjustment for age, smoking, hypercholesterolemia, hypertension, and diabetes mellitus. In contrast, obesity was not associated with an increased risk for AMI in females or in older or very old males. Smoking was a significant risk for AMI in middle-aged and older females, as well as in older males, after adjustment for age, obesity, hypercholesterolemia, hypertension, and diabetes mellitus (Table 2). In contrast, smoking was not associated with an increased risk for AMI in young, middle-aged or very old males, or in very old females.

Discussion

The major findings of the present multicenter case–control study in Japan are: (1) obesity was an independent risk for AMI in young and middle-aged males, but not in females; and (2) smoking was an independent risk for AMI in middle-aged and older females, as well as in older males.

Although the data regarding the association of obesity with atherosclerosis and CHD have been inconsistent for many years,10,11 recent accumulating evidence indicates that obesity is an independent CHD risk factor among adults.12 There have also been conflicting data regarding the relationship between obesity and CHD in Japan13–18 Some prospective studies have revealed that obesity is a CHD risk factor after adjusting for other risk factors, in Japan as well as in Western countries;13,14 but other case–control studies have not found the same result.15–17 However, a recent case–control study has indicated that past obesity is a CHD risk factor, even after weight reduction.18 In the present report, we have also shown that obesity is a CHD risk factor in young and middle-aged males, but not in females or older males. The age- and gender-related differences in the CHD risk associated with obesity might contribute, at least in part, to these conflicting data.

As for young adults, there have also been inconsistent data regarding the effects of obesity on CHD. A previous prospective study in the United States showed that among males younger than 65, BMI had a significant positive association with the CHD risk, but the association was much weaker among older males aged 65 years or more.19 In contrast, another case–control analysis of people aged 30–60 years in India indicated no association between BMI and AMI.20 A recent report indicated a significant relationship between obesity and coronary atherosclerosis in young male adults, particularly in those with central obesity, and little relationship between them in young female adults.21 Still other recent clinical studies have also shown that obesity and its metabolic impairment (ie, metabolic syndrome) are associated with impaired endothelial function and early atherosclerotic change in adolescents.22–24 However, there are no data regarding the association of obesity with atherosclerosis and CHD in Japanese young adults. Recently, we showed that young Japanese patients with AMI have a higher BMI than older patients and in the present report, we have demonstrated for the first time that obesity is an independent AMI risk factor in young and middle-aged Japanese males.

In the present report, the susceptibility to AMI from the risk of obesity or smoking differed between males and females. A previous study has shown that the relative CHD risk associated with obesity in middle-aged and older females is slightly lower than that for males.25 The sex difference in the effect of obesity on CHD might be derived from the pattern of fat distribution. Although at an equivalent BMI, females at all ages have a larger percentage of body fat than male;26 males are more prone to have a central (visceral) pattern of fat distribution.26 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 rather than peripheral obesity.25–27 Another possible explanation is the protective effects of female hormones against CHD progression in the premenopausal woman. In the present study, AMI cases had a significantly greater BMI than control subjects in the older female group, but there was no significant difference in BMI between AMI cases and control subjects among middle-aged females. We can
not rule out the possibility that an increased prevalence of obesity after menopause, together with hypercholesterolemia, hypertension, and diabetes mellitus might also contribute, in part, to the etiology of CHD in older women.

On the other hand, our present study has indicated that smoking is a more independent and more significant risk factor for AMI in middle-aged and older females than in males, which is consistent with a recent report from Japanese investigators. However, the mechanism for a gender difference in the effects of smoking remains to be elucidated. In general, females tend to be more susceptible to the respiratory disorders ascribed to smoking, such as asthma, bronchitis, and emphysema, than males. Thus, it is reasonable to propose that females might be more sensitive to the effects of smoking on CHD than males.

Our results have shown that obesity is an independent risk for AMI in young and middle-aged males, not older or very old males. The reason for this age-related variability in the effect of obesity on AMI remains unclear. Older obese men may have a higher prevalence of hypertension or diabetes mellitus than younger obese ones. Thus, in the present study, adjusting for other risk factors might make the AMI risk associated with obesity more difficult to detect in the older men. Another possible explanation is that the increasing prevalence of obesity might make the risk easier to detect in young adults with CHD. The other possible explanation is that metabolic syndrome, accompanied by obesity, particularly visceral obesity, might play a central role in the pathogenesis of AMI in young male adults with a lower incidence of co-morbid diseases such as diabetes mellitus and hypertension. Findings from previous reports and our present study support the current emphasis on control of obesity, particularly visceral obesity, to prevent CHD in young adult males.

Study Limitations

First, there is a time-delay (approximately 1–4.5 years) between the data for the case subjects and that for the control subjects. Second, there is a difference in the mean age (approximately 4 years or less) between the cases and the controls. Third, the present study population consisted of AMI patients who were admitted to collaborating hospitals and residents in Kyoto Prefecture, so it might not reflect the situation for the entire Japanese population. Fourth, data regarding risk factors and BMI were not available for all AMI patients. Further prospective studies or more precisely controlled case–control studies are needed to elucidate the CHD risk associated with obesity in Japan.

Conclusion

The present study provides evidence that obesity is an independent risk for AMI in young and middle-aged Japanese males, suggesting that it is necessary to correct obesity for primary prevention of AMI in young male adults in Japan. However, the relatively small sample size is a major limitation and a larger study should be performed to confirm our findings.

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**Appendix 1**

The following institutions and principal investigators participated in the present study as the AMI-Kyoto Multi-Center Risk Study Group.