Past History of Obesity (Overweight by WHO Criteria) Is Associated With an Increased Risk of Nonfatal Acute Myocardial Infarction — A Case–Control Study in Japan —

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Background Obesity is an important risk factor for the occurrence of coronary artery disease (CAD) in Western countries and furthermore, it often coexists with other CAD risk factors such as hypertension, dyslipidemia and diabetes mellitus. However, it is uncertain whether obesity is a CAD risk factor in Japan because Japanese are relatively thin on average.

Methods and Results The CAD risk associated with obesity (body mass index $\geq 25.0$) 10 years before as well as at the time of the survey was assessed in a case–control study of acute myocardial infarction (AMI), which compared 660 AMI patients aged 40–79 years and 1,277 community controls, matched to each case by sex, year of birth, and residence. The prevalence of current obesity did not show any material difference between cases and controls, but compared with controls, past obesity was much more frequent in cases. Even after controlling for other CAD risk factors, past obesity was associated with a 2-fold increase in the risk of AMI. Past obesity was associated with an increased risk of AMI even without current obesity.

Conclusion Past obesity is a CAD risk, even after weight reduction. (Circ J 2004; 68: 41–46)

Key Words: Myocardial infarction; Obesity; Overweight; Weight change

Coronary artery disease (CAD) is the single most important disease entity in Western countries and obesity is a risk factor for the occurrence of clinical coronary events. Furthermore, obesity often coexists with other CAD risk factors, such as hypertension, dyslipidemia and diabetes. The prevalence of ‘obesity’ by the World Health Organization criterion (body mass index (BMI) $\geq 30.0$) is low (3%) in Japan by comparison (eg, 8% in Sweden, 20% in UK, 23% in USA) but it has rapidly increased with the westernization of the Japanese life style, including dietary habits which has brought on other CAD risk factors associated with insulin-resistance syndrome, such as hypertension, dyslipidemia and diabetes. Kaplan proposed the term ‘deadly quartet’ for the profile of a person with the very high CAD risk of the combination of upper body obesity, hypertension, hypertriglyceridemia and impaired glucose tolerance.

The WHO Expert Committee in 1995 proposed the term of ‘overweight’ (BMI $\geq 25.0$) and drew special attention to the health effect of overweight in the association with increased mortality. More than half of the adult population in Western countries are ‘overweight’ and 20–25% in Japan come into that category. However, because ‘obesity’ based on a BMI of 30.0 or greater is low in Japan; the Japanese Society for the Study of Obesity redefined it as a BMI of 25.0 or greater. Furthermore, ‘BMI $\geq 25.0$’ is a useful standard for identifying diabetes risk in Japanese-Americans. Therefore, we will use the definition of obesity of the Japanese Society for the Study of Obesity rather than that of the WHO.

Japanese investigators have shown that obesity is a CAD risk factor in Japan as well as in Western countries; however, only the cohort studies have shown that obesity is a CAD risk factor after adjusting for other CAD risk factors, the case–control studies do not. A follow-up study of Japanese CAD patients shows that obesity is an independent risk factor for coronary events.

The Framingham Heart Study shows that obesity is a CAD risk factor at 14-, 20- or 26-year follow-up periods, but not at 6- or 8-year follow-up. Thus, we assessed the CAD risk in relation to present and past obesity in a case–control study of acute myocardial infarction (AMI).

Methods

Cases and Controls


Cases and Controls

The selection criteria and study design of the Fukuoka Heart Study have been described previously. Eligible cases were patients aged 40–79 years who were admitted to 22 hospitals in Fukuoka City and adjacent municipalities for a first AMI during September 1996 to September 1998 and who recovered well enough to be interviewed within 1 month of the onset of AMI.

Research nurses visited each hospital weekly, checked all admissions with a diagnosis of AMI or suspected AMI,
and asked eligible patients to participate in the study. Collaborating cardiologists were in charge of the diagnosis of AMI, which was based on the electrocardiogram, ischemic cardiac pain lasting at least 30 min, and enzyme changes. Of 756 eligible patients, a total of 660 (87%) participated in the study. Reasons for non-participation were impaired ability to communicate (n=9), discharge before interview (n=65), and refusal (n=22). Eighteen cases were excluded in the analysis because their serum total cholesterol values (n=2) or body weight 10 years before the survey (n=65), and refusal (n=22). Eighteen nonparticipating (52%) of 2,433 control candidates were used for the analysis before the survey were not available.

One or 2 controls matched to each case for sex, year of birth (within 2 years), and proximity in residence were surveyed. Control candidates selected from the resident registers were first approached by mail. Two reminders were sent, and contact by telephone was attempted last. A total of 2,913 control candidates were approached between September 1996 and March 1999. The outcome of recruiting controls was as follows: undelivered mail 53, deceased 22, nonresident 26, prior history of myocardial infarction 79, refusal 22, nonparticipating (52%) of 2,433 control candidates were used for the analysis before the survey (n=16) were not available.

Thus, 650 (86%) of 756 eligible patients and 1,271 (52%) of 2,433 control candidates were used for the analysis in this study. As reported previously nonparticipating control candidates were almost similar in characteristics to control subjects.

Behavioral and Clinical Risk Factors

A questionnaire survey was used to ascertain personal characteristics, life style habits, such as smoking, consumption of alcohol and physical activity, and medical history of angina pectoris, hypertension, diabetes mellitus and hypercholesterolemia, and body weight 10 years before the survey. Details of the interview survey have been reported elsewhere. While they were in hospital, the patients were given the questionnaire and interviewed by the research nurses. The questionnaires were mailed to control subjects and then the research nurses and members of the working group (physicians and a public health nurse) interviewed them at a clinic if they were under medical supervision, at work, at home or at Kyushu University.

Research nurses checked the medical records of cases to ascertain current medication prior to the AMI, height, body weight, and the serum concentration of total cholesterol measured during admission. When blood had not been taken within 24 h of the onset of AMI, the primary physician was asked about serum lipid measurements immediately after, or alternatively before, the onset of AMI.

For the controls, a nonfasting, venous blood sample was taken for determination of serum lipids in the Clinical Laboratory of the Fukuoka City Medical Association. If serum total cholesterol had been measured within 6 month before interview, the recorded data were obtained from the subjects or their physicians. Height and weight were measured for most of controls, but self-reported values were obtained from some of controls interviewed at their home or work place. Current medication was also elicited by referring to medical records at clinics.

Hypertension and angina pectoris were defined as present when subjects were under drug treatment. Subjects under dietary or drug treatment for diabetes mellitus were classified as having the disease. Hypercholesterolemia was considered present if subjects were under drug treatment. Subjects or their physicians viewed them at a clinic if they were under medical supervision. Height and weight were measured during admission. When blood had not been taken within 24 h of the onset of AMI, the primary physician was asked about serum lipid measurements immediately after, or alternatively before, the onset of AMI.

**Statistical Analysis**

Conditional logistic regression analysis was used to make adjustments for potential confounding variables. Covariates included in the model were age, life style (ie, smoking, drinking, leisure-time physical activity), and medical history (ie, angina pectoris, diabetes mellitus, hypertension, and hypercholesterolemia). The subjects who had ever smoked every day over a period of 1 year or longer, moderate or more active exercise for 30 min or more per week.

<table>
<thead>
<tr>
<th>Table 1 Characteristics of the Cases and Controls</th>
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<tbody>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td>n=650</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Elderly (&gt;65 years)</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg) at time of survey</td>
</tr>
<tr>
<td>Weight (kg) 10 years before survey</td>
</tr>
<tr>
<td>Obesity at time of survey</td>
</tr>
<tr>
<td>Obesity 10 years before survey</td>
</tr>
<tr>
<td>Life style</td>
</tr>
<tr>
<td>Smokers</td>
</tr>
<tr>
<td>Drinkers</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
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Values are expressed as mean±SD or number (%).

*body mass index ≥25.0, †smoked every day over a period of 1 year or longer, ‡drunk alcohol once per week over a period of 1 year or longer, †±moderate or more active exercise for 30 min or more per week.*
Results

Table 1 shows the characteristics of the cases and controls. Compared with controls, body weight and the prevalence of obesity 10 years before the survey were greater in cases, less cases smoked and drank and more of the cases had low leisure-time physical activity. More cases were diagnosed as having angina pectoris, hypertension, diabetes mellitus or hypercholesterolemia.

As shown in Table 2, obesity 10 years before the survey increased the risk of AMI in both men and women whereas present obesity failed to do so. Obesity 10 years before the survey was associated with an increased OR in both sexes. It remained a significant risk factor even after controlling age, life style (ie, smoking, drinking and leisure-time physical activity) and medical history (ie, angina pectoris, hypertension, diabetes mellitus or hypercholesterolemia) in men, but failed to do so after controlling age and medical history in women.

Table 3 shows the ORs of AMI of middle-aged and elderly persons. Present obesity was not associated with an increased risk of AMI. In contrast, obesity 10 years before the survey increased the risk of AMI in the 2 age groups after adjusting for age and life style and age and medical history. Even after controlling for age, life style and medical history, obesity 10 years before the survey showed a significantly increased OR in the elderly, but a marginally increased OR in the middle-aged.

As shown in Table 4, past obesity without current obesity was associated with an increased risk of AMI even after controlling for age, lifestyle and medical history while past obesity with current obesity was associated with an increased risk of AMI even after controlling for age and lifestyle but failed to do so after controlling for medical history. In contrast, current obesity without past obesity was associated with a decreased risk of AMI even after controlling for age, life style and medical history.

Discussion

There are several reports showing that obesity is a CAD risk factor in Japan6,7,13–16 and Western countries1–6. However, there are some that show obesity is not a risk factor among the Japanese population21,22. The failure of obesity as a CAD risk factor in those studies may be partly explained by the low prevalence of obesity among Japanese6.

In a cross-sectional study of Japanese23, BMI was predic-
tive of coronary stenosis among male patients, but not female patients, who underwent angiography because of clinical signs of coronary heart disease. Both cross-sectional and case-control studies have a weakness for showing the association between obesity and CAD. Most high-risk subjects, such as those with obesity and multiple CAD risk factors, might have died or suffered from CAD before the study because obesity often coexists with other CAD risk factors associated with insulin-resistance syndrome, such as hypertension, dyslipidemia and diabetes.1,2,6–8 A positive correlation between the frequency of insulin resistance and the accumulation of CAD risk factors has been observed in a Japanese community.24 In addition, changes in body weight are significantly related to changes in other CAD risk factors, such as blood pressure, fasting blood glucose, serum cholesterol, serum triglyceride and serum uric acid.25 For this reason, obese individuals need to reduce their weight to improve their health. Only subjects who had reduced their body weight, and therefore the other CAD risk factors, might have been free of CAD and able to participate in this study, which may be another explanation of why past obesity was a CAD risk factor whereas current obesity at the time of survey was not. This is not contrary to the results of the cohort studies, which show that obesity is a CAD risk factor3–5,7,15,16 The Framingham Heart Study3 shows that obesity is a CAD risk factor at the 14-, 20- or 26-year follow-up, but not at the 6- or 8-year follow-up periods. Thus, only long lasting obesity may increase the risk of AMI. A case-control study in India showed no association between BMI and AMI among subjects aged 30–60 years,26 and another in the United States reported that BMI was rather lower in cases than controls among subjects aged 65 years or older.27 Those reports support the result of the present study.

Past obesity remained as a significant CAD risk factor even after controlling other CAD risk factors in men, but failed to do so after in women, which may be partly explained by the fact that the number of female study subjects was small. Another explanation is that metabolic disorders such as diabetes mellitus show a higher CAD risk in women than men.28,29 In the present study, past obesity was associated with an increased risk of AMI in the 2 age groups after adjusting for age and lifestyle. Even after controlling for age, lifestyle and medical history, past obesity showed a significantly increased OR in the elderly, but a marginally increased OR in the middle-aged. This may be partly explained by the possibility that those with obesity might have died or suffered from CAD when younger or middle-aged. Another explanation is that the older, more obese subjects may be a select group who are resistant to the influence of obesity during their earlier years.

Although the Framingham study30 demonstrated that weight reduction decreases other CAD risk factors, such as hypertension, dyslipidemia, diabetes and hyperuricemia, the present study revealed that past obesity without current obesity was an independent CAD risk factor. The result of the present study suggests that past obesity is a CAD risk even after weight reduction.

On the other hand, past obesity with current obesity was

<table>
<thead>
<tr>
<th>n = 481</th>
<th>n = 949</th>
<th>p value</th>
<th>n = 169</th>
<th>n = 322</th>
<th>p value</th>
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<tr>
<td>n = 169</td>
<td>n = 322</td>
<td>p value</td>
<td>n = 169</td>
<td>n = 322</td>
<td>p value</td>
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<table>
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<tr>
<th>Obesity 10 years before survey</th>
<th>Without</th>
<th>With</th>
<th>p value</th>
<th>Without</th>
<th>With</th>
<th>p value</th>
</tr>
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<tr>
<td>With</td>
<td>88 (18.3%)</td>
<td>97 (10.2%)</td>
<td>&lt;0.0001</td>
<td>133 (78.7%)</td>
<td>200 (62.1%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Without</td>
<td>393 (81.7%)</td>
<td>852 (89.8%)</td>
<td>p&lt;0.001</td>
<td>36 (21.3%)</td>
<td>122 (37.9%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>p value with obesity vs without obesity at time of survey</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
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</table>

*BMI ≥ 25.0.
associated with an increased OR of AMI, but failed to remain so after adjusting for other CAD risk factors. These findings may be caused partly by over-adjustment because obesity often coexists with other CAD risk factors. Another possibility is that those with obesity both 10 years before and at the survey may be a select group, who were free of CAD during those 10 years in spite of the influence of obesity. Obese subjects without resistance to the influence of obesity may have suffered from CAD within the 10 years. In contrast, current obesity without past obesity was associated with a decreased risk of AMI, for which there are 3 explanations. First, only long-lasting obesity may worsen coronary atherosclerosis, which is consistent with the result of the Framingham Heart Study in which obesity was shown to be a CAD risk factor at the 14-year follow-up period or more, but not at 8 years or less. Second, unless they have resistance to the influence of obesity, those with newly developed obesity might have died or suffered from CAD during the 10 years. Thus, the underestimated risk of AMI may lead to the opposite result. Finally, there is the chance phenomenon. In the present study, a quarter of both the cases and controls were fat (Table 1). As shown in Table 5, most of the obese subjects answered at the time of the survey that they had been fat 10 years before. There were only 36 obese cases and 122 obese controls without past obesity. That small number of subjects may cause the chance phenomenon.

Very recently, the Japanese Society for the Study of Obesity proposed a new criterion for ‘obesity disease’ in Japan. They showed that the number of obesity-related complications, such as hyperglycemia, dyslipidemia and hypertension, increased in accordance with BMI and those with a BMI ≥ 25 had more than twice the CAD risk. In the definition of ‘obesity disease’ is obesity with complications that require weight reduction for their improvement or elimination, which is consistent with both the definition of ‘overweight’ by The WHO Expert Committee in 1995 and the Guideline for Primary Prevention of Ischemic Heart Disease from the Japanese Circulation Society.

In summary, the present study revealed that past obesity was associated with an increased risk of AMI. Compared with Western countries, the incidence of CAD is very low in Japan; however, the NI-HON-SAN study demonstrated that a change to a Western life style resulted in an increase in CAD among Japanese-Americans. Because our results suggest the past obesity increases the CAD risk, even after the weight reduction, public health education systems should be implemented to avoid obesity in both younger and the middle-aged Japanese.

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References


**Appendix 1**

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