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RISK FACTORS FOR FIRST ACUTE MYOCARDIAL INFARCTION ATTACK ASSESSED BY CARDIOVASCULAR DISEASE REGISTRY DATA IN AICHI PREFECTURE

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ABSTRACT

Recently, in Western countries, metabolic syndrome as well as such classical risk factors as hypertension and smoking has been considered to be closely associated with the occurrence of acute myocardial infarction (AMI). Therefore, we conducted a case-control study to investigate how the co-morbidity of obesity or thinness with hypertension, hyperlipidemia and diabetes mellitus would affect AMI occurrence among Japanese aged 30 to 69. Cases were comprised of 788 patients (590 men and 198 women) registered in the "Aichi Prefecture Cardiovascular Disease Registry Program" during hospitalization due to their first AMI attack. Controls were 2,300 randomly sampled inhabitants (1,142 men and 1,158 women) who responded to the questionnaire survey on lifestyle. We decided BMI$<$18.5 as thin, 18.5$\leqq$BMI$<$25.0 as normal, and BMI$\geqq$25.0 as obese, then divided subjects into six groups according to the presence or absence of histories of the above-mentioned three diseases in connection with their physique. In both sexes, multivariately adjusted odds ratios of first AMI attacks were much higher in groups with such histories (men, 4.14~5.07; women, 5.62~15.24) than in those without them (men, 0.90~1.13; women, 1.54~3.03) regardless of physique. Only in women, obesity uncombined with histories was significantly associated with AMI occurrence and not obesity but thinness intensified the association between histories and AMI. Among the six groups, population attributable risk percent was highest in the normal physique group with histories. It was suggested that persons with disease histories should be carefully treated irrespective of the presence or absence of obesity.

Key Words: Acute myocardial infarction, Disease history, Obesity, Thinness, Cardiovascular disease registry

INTRODUCTION

Since the Aichi Prefectural Government established the "Healthy Japan 21 Aichi Project"[1)] in 2001, it has carried out various programs to prevent lifestyle-related diseases such as

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acute myocardial infarction (AMI). As one of the programs, it started the "Aichi Prefecture Cardiovascular Disease Registry Program"[2] in 2001 to register myocardial infarction or stroke patients' lifestyle and disease histories of hypertension, hyperlipidemia and diabetes mellitus, and conducted surveys on inhabitants' lifestyle.[3,4] The Ministry of Health, Labour and Welfare has plans to begin health checkups in 2008 to select individuals with metabolic syndrome and to provide personalized health educational programs to help them improve their lifestyle.[5] Although previous studies have demonstrated that disease histories of hypertension and hyperlipidemia and lifestyle such as smoking are important risk factors for AMI,[6] metabolic syndrome, which is caused by obesity, has been reportedly associated with AMI in Western countries.[7,8] Would this be true for Japan as well? To answer this question, we conducted a case-control study to clarify the relationships between AMI occurrence and each of the classical risk factors including hypertension, hyperlipidemia and diabetes mellitus as well as their co-morbidity among Japanese people. But here our objective was to determine how obesity or thinness might affect this set of relationships by calculating odds ratios (OR) and population attributable risk percent (PARP).[9]

SUBJECTS AND METHODS

Cases were a total of 788 (590 men and 198 women) who completed the registry form, out of 2,034 AMI patients aged 30 to 69 (1,546 men and 488 women) admitted to hospitals in Aichi Prefecture between 2001 and 2004 in connection with their first attack and registered in the "Aichi Prefecture Cardiovascular Disease Registry Program." The Aichi Prefectural Government conducted lifestyle surveys by mail in 2000 and 2004 among inhabitants aged 16 years or older who were randomly selected at a sampling rate of one out of 500 for those aged 16 to 19 and one out of 1,000 for those aged 20 years or older. Controls were 2,300 inhabitants (1,142 men and 1,158 women) among the respondents to this survey without a history of angina pectoris or AMI aged 30 to 69, who answered all the questions in the self-reported questionnaire.

We used case information on sex, birth-year, date of attack, alcohol consumption, exercise, smoking, physique (height, weight), and histories of hypertension, hypercholesterolemia and diabetes mellitus on the registry form. For controls, we used corresponding information from the questionnaire entitled "Survey on Lifestyle in Aichi Prefecture."

In analyzing data, we categorized response choices in the questionnaire as follows. In cases, current drinkers were defined as those who drank more than 20 g ethanol per day, and ex-drinkers and never-drinkers were taken as non-drinkers. In controls, subjects who replied "drink every day," "drink five or six days a week," "drink three or four days a week" or "drink one or two days a week" were taken as current drinkers, while those who replied "drink one or two days a month," "seldom drink" and "ex-drinkers" were taken as non-drinkers. Among the cases, subjects who replied "walk for half an hour three days a week," or "walk for half an hour one or two days a week," were taken as having the exercise habit, and those who replied "rarely (one or two days a month)" were taken as not having the exercise habit. In controls, those who answered that they "exercised more than half an hour two days a week for a year or more" and "exercised more than half an hour two days a week for less than a year" were taken as having the exercise habit, and those replying "do not do such exercise" were taken as not having the exercise habit. We categorized both cases and controls into smokers and non-smokers which included ex-smokers.

Although questions regarding histories of ten diseases, including hyperlipidemia, hypertension and diabetes mellitus were asked in controls, cases were asked about histories of hypercholesterolemia instead of hyperlipidemia, in addition to hypertension and diabetes mellitus. Thus,

we conveniently took both hypercholesterolemia and hyperlipidemia to represent either or both elevated serum cholesterol and triglyceride. Since type IIb hyperlipidemia is known as one of the frequent phenotypes, it is likely that patients with hypercholesterolemia may also have elevated triglyceride. Furthermore, familial combined hyperlipidemia was reported to be most frequent among the survivors of myocardial infarction.[10] BMI (Body Mass Index) was calculated as weight in kilograms divided by the square of height in meters, BMI $<$ 18.5 was decided as thin, 18.5 $\leqq$ BMI $<$ 25.0 as normal, and BMI $\geqq$ 25.0 as obese. To assess whether the relationships between the number of disease histories of hypertension, hyperlipidemia and diabetes mellitus and the occurrence of AMI were affected by obesity or thinness, we divided subjects into six groups: 1) group with none of the three diseases with neither obesity nor thinness; 2) group with none of the three diseases but with thinness; 3) group with none of the three diseases but with obesity; 4) group with some of the three diseases but with neither obesity nor thinness; 5) group with some of the three diseases and thinness; and 6) group with some of the three diseases and obesity.

The χ^2 test was used to compare the proportions of lifestyle factors such as alcohol consumption, exercise and smoking, physique and disease histories between cases and controls for each sex. Physique, hypertension, hyperlipidemia and diabetes mellitus are widely known to be closely associated not only with one another but also with age and lifestyle. To evaluate the effects of these factors on AMI attack by adjusting for the effects of their mutual confoundings, we calculated ORs for AMI occurrence using unconditional multiple logistic regression analysis based on a case-control study. To examine the magnitude of the effect of risk factors on AMI occurrence by taking into account the prevalence of the risk factors in controls, we also calculated the PARP for AMI for each of the above six groups by using the group with none of the three diseases with neither obesity nor thinness as the reference group. All statistical analyses were performed using SPSS software, version 12.0 J for Windows. A p-value $<$ 0.05 by two-tailed test was considered statistically significant.

RESULTS

Table 1 shows the number of subjects according to age. Among male cases, the 60 to 69 group had the largest number of subjects (310, 52.5%), and more than 85% of total male cases were older than 50 years. The number of subjects gradually decreased as the age declined. In male controls, the distribution by age was not as uneven as in male cases, but there were more older subjects. In men, the mean age $\pm$ SD was 58.39 $\pm$ 8.33 years for cases and 52.64 $\pm$ 10.68 years for controls. In women, the mean age $\pm$ SD was 60.07 $\pm$ 7.83 years for cases and 50.34 $\pm$ 10.99 years for controls. The age-related increase in the proportion of cases was more conspicuous in women than in men, whereas in the proportion of controls it was less so.

Table 1 Number of subjects according to age

Sex		Age (Years) 30–39	40–49	50–59	60–69	Total	Mean $\pm$ SD
Men	Cases	21 (3.6%)	60 (10.2%)	199 (33.7%)	310 (52.5%)	590 (100.0%)	58.39 $\pm$ 8.33
	Controls	169 (14.8%)	249 (21.8%)	361 (31.6%)	363 (31.8%)	1142 (100.0%)	52.64 $\pm$ 10.68
Women	Cases	3 (1.5%)	16 (8.1%)	53 (26.8%)	126 (63.6%)	198 (100.0%)	60.07 $\pm$ 7.83
	Controls	244 (21.1%)	272 (23.5%)	349 (30.1%)	293 (25.3%)	1158 (100.0%)	50.34 $\pm$ 10.99

Table 2 Characteristics of cases and controls

Sex	Factors	Cases	Controls	P
Men	Alcohol	191 (32.4%)	710 (62.2%)	<0.001
	Exercise	285 (48.3%)	368 (32.2%)	<0.001
	Smoking	295 (50.0%)	489 (42.8%)	<0.01
	BMI (Mean±SD)	23.49±5.53	23.21±3.12	ns#
	BMI (Thin)	28 (4.7%)	59 (5.2%)	ns$
	BMI (Normal)	386 (65.4%)	797 (69.8%)	
	BMI (Obese)	176 (29.8%)	286 (25.0%)	
	Hypertension	286 (48.5%)	265 (23.2%)	<0.001
	Hyperlipidemia	218 (36.9%)	141 (12.3%)	<0.001
	Diabetes mellitus	179 (30.3%)	114 (10.0%)	<0.001
Women	Alcohol	42 (21.2%)	261 (22.5%)	ns
	Exercise	78 (39.4%)	367 (31.7%)	<0.05
	Smoking	94 (47.5%)	140 (12.1%)	<0.001
	BMI (Mean±SD)	23.49±4.58	21.91±3.39	<0.001#
	BMI (Thin)	18 (9.1%)	119 (10.3%)	<0.001$
	BMI (Normal)	116 (58.6%)	870 (75.1%)	
	BMI (Obese)	64 (32.3%)	169 (14.6%)	
	Hypertension	102 (51.5%)	231 (19.9%)	<0.001
	Hyperlipidemia	86 (43.4%)	117 (10.1%)	<0.001
	Diabetes mellitus	69 (34.8%)	49 (4.2%)	<0.001

P: probability of difference between cases and controls by χ^2 test
ns: $p>0.1$
( ): percent of total cases or controls in each sex
#: t test
$: χ^2 test for 2 by 3 cells

Table 2 shows other characteristics of cases and controls. In men, the proportion of alcohol drinkers was significantly smaller, while that of those who exercised or smoked was significantly larger in cases than in controls. The mean BMI±SD was 23.49±5.53 kg/m^2 in cases and 23.21±3.12 kg/m^2 in controls, with no statistically significant difference. Although obesity was more prevalent in cases than in controls (29.8% vs 25.0%), there was no significant difference by the χ^2 test for 2 by 3 cells. Hypertension (48.5% vs 23.2%, $p<0.001$), hyperlipidemia (36.9% vs 12.3%, $p<0.001$) and diabetes mellitus (30.3% vs 10.0%, $p<0.001$) were all significantly more prevalent in cases than in controls. In women, the proportion of those who exercised or smoked was significantly larger in cases than in controls, while that of alcohol drinkers showed no statistically significant difference between cases and controls. The mean BMI was significantly greater in cases than in controls (mean±SD : 23.49±4.58 kg/m^2 vs 21.91±3.39 kg/m^2, $p<0.001$). The distribution of physique was significantly different between cases and controls by the χ^2 test, and obesity was more prevalent in cases than in controls (32.3% vs 14.6%, $p<0.001$) while thinness was not (9.1% vs 10.3%). Hypertension (51.5% vs 19.9%, $p<0.001$), hyperlipidemia (43.4% vs 10.1%, $p<0.001$) and diabetes mellitus (34.8% vs 4.2%, $p<0.001$) were all significantly more prevalent in cases than in controls.

Table 3 shows multivariately adjusted ORs for AMI occurrence according to physique and disease histories. In men, obesity and the respective histories of hypertension, hyperlipidemia and diabetes mellitus were all significantly associated with AMI occurrence, whereas thinness was not

Table 3 Multivariately adjusted ORs for AMI occurrence according to physique and disease histories

Sex	Factors	ORa	ORb	ORc
Men	BMI (Thin)	0.98 [0.60–1.58]	0.90 [0.54–1.49]	0.93 [0.54–1.61]
	BMI (Normal)	1.00 [referent]	1.00 [referent]	1.00 [referent]
	BMI (Obese)	1.39 [1.10–1.76]*	1.40 [1.09–1.80]*	1.04 [0.80–1.37]
	Hypertension	2.71 [2.18–3.38]***	3.14 [2.47–3.98]***	2.58 [2.01–3.32]***
	Hyperlipidemia	4.01 [3.12–5.16]***	4.18 [3.20–5.47]***	3.26 [2.45–4.33]***
	Diabetes mellitus	3.40 [2.60–4.45]***	3.40 [2.56–4.52]***	2.69 [1.99–3.64]***
Women	BMI (Thin)	1.49 [0.84–2.65]	1.62 [0.88–2.98]	1.94 [1.01–3.75]$^{+}$
	BMI (Normal)	1.00 [referent]	1.00 [referent]	1.00 [referent]
	BMI (Obese)	2.27 [1.57–3.28]***	2.21 [1.48–3.31]***	1.92 [1.21–3.04]*
	Hypertension	2.57 [1.85–3.59]***	2.92 [2.03–4.22]***	2.10 [1.39–3.18]***
	Hyperlipidemia	5.22 [3.64–7.48]***	6.60 [4.40–9.90]***	5.58 [3.59–8.67]***
	Diabetes mellitus	8.14 [5.29–12.53]***	8.01 [5.02–12.80]***	6.24 [3.75–10.40]***

$^{+}$: $p<0.1$, *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$
(after correction for multiplicity of comparison by Bonferroni method)
[ ]: 95% confidence intervals
ORa: odds ratio adjusted for age
ORb: odds ratio adjusted for age, alcohol, exercise and smoking
ORc: odds ratio adjusted for age, alcohol, exercise, smoking, hypertension, hyperlipidemia and diabetes mellitus

when adjusted for age (ORa) or age and lifestyle (ORb). When adjusted for age, lifestyle and disease histories, obesity was not a significant risk factor (ORc: 1.04, $p>0.1$), though all of the disease histories were significantly associated with AMI (ORc: hypertension, 2.58; hyperlipidemia, 3.26; and diabetes mellitus, 2.69, $p<0.001$ for all). In women, obesity and all of the disease histories were significantly associated with AMI occurrence, but thinness was not when adjusted for age (ORa) or age and lifestyle (ORb), as was true among men as well. However, when adjusted for age, lifestyle and disease histories, obesity (ORc: 1.92, $p<0.05$) and the respective histories of hypertension, hyperlipidemia and diabetes mellitus were still significantly associated with AMI occurrence (ORc : hypertension, 2.10; hyperlipidemia, 5.58; and diabetes mellitus, 6.24, $p<0.001$ for all). Thinness was borderline significantly associated with AMI (ORc: 1.94, $p<0.1$).

Table 4 shows the prevalence and multivariately adjusted ORs for AMI occurrence according to the combination of physique and disease histories. In men, ORds obtained by adjusting for age were significantly higher than unity in the groups with histories (ORd: thin, 4.94; normal, 3.83; obese, 4.42, $p<0.001$ for all, corrected for multiplicity of comparison by Bonferroni method). However, all ORds were insignificant in the groups without histories (ORd: thin, 0.90; obese, 1.24, $p>0.1$ for both). The result was almost the same even when adjusted for age and lifestyle, as shown by ORes in Table 4.

In women, as in men, ORds obtained by adjusting for age were significantly higher than unity in the groups with histories (ORd: thin, 8.61; normal, 4.55; obese, 6.77, $p<0.001$ for all, after Bonferroni correction). Although ORd of the thin group without histories (1.53) was insignificant, that of the obese group without histories was significantly greater than unity (ORd: 3.23, $p<0.01$, after Bonferroni correction), in contrast to men. The result was almost the same even when adjusted for age and lifestyle, as shown by ORes in Table 4. However, ORe of

Table 4 Prevalence and multivariately adjusted ORs for AMI occurrence according to combination of physique and disease histories

Sex	Physique	Disease history							
		Absent				Present			
		Cases	Controls	ORd	ORe	Cases	Controls	ORd	ORe
Men	Thin	9 (1.5%)	44 (3.9%)	0.90 [0.42–1.92]	0.90 [0.40–1.99]	19 (3.2%)	15 (1.3%)	4.94 [2.39–10.20]***	4.14 [1.95–8.79]**
	Normal	115 (19.5%)	530 (46.4%)	1.00 [referent]	1.00 [referent]	271 (45.9%)	267 (23.4%)	3.83 [2.93–5.02]***	4.27 [3.19–5.70]***
	Obese	39 (6.6%)	149 (13.0%)	1.24 [0.82–1.88]	1.13 [0.73–1.76]	137 (23.2%)	137 (12.0%)	4.42 [3.21–6.09]***	5.07 [3.60–7.15]***
Women	Thin	6 (3.0%)	98 (8.5%)	1.53 [0.61–3.87]	1.54 [0.58–4.12]	12 (6.1%)	21 (1.8%)	8.61 [3.71–19.98]***	15.24 [6.02–38.58]***
	Normal	31 (15.7%)	636 (54.9%)	1.00 [referent]	1.00 [referent]	85 (42.9%)	234 (20.2%)	4.55 [2.89–7.16]***	5.62 [3.42–9.25]***
	Obese	15 (7.6%)	82 (7.1%)	3.23 [1.64–6.37]**	3.03 [1.42–6.45]*	49 (24.7%)	87 (7.5%)	6.77 [4.01–11.42]***	8.13 [4.55–14.54]***

*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$ (after correction for multiplicity of comparison by Bonferroni method)
[ ]: 95% confidence intervals
( ): percent of total cases or controls in each sex
ORd: odds ratio adjusted for age
ORe: odds ratio adjusted for age, alcohol, exercise and smoking

Table 5 PARP for AMI occurrence in six groups in present survey

Sex	Physique	Disease history			
		Absent		Present	
		Pe	PARP	Pe	PARP
Men	Thin	0.0385	–0.2	0.0131	1.8
	Normal	0.4641	referent	0.2338	33.1
	Obese	0.1305	0.7	0.1200	21.2
Women	Thin	0.0846	1.6	0.0181	8.8
	Normal	0.5492	referent	0.2021	32.0
	Obese	0.0708	4.9	0.0751	18.4

Pe: proportion of the exposed among controls
PARP: population attributable risk percent

the thin group with histories was disproportionately larger (15.24, $p<0.001$) than what might be expected as the product of ORes of thinness and histories (1.54, 5.62, respectively). When an interaction term between physique and disease histories was included in the model without adjustment factors, it was shown that the interaction was present in women ($p=0.061$). When only age or age and lifestyle were further included, the presence of interaction was still suggested ($p=0.132$, $p=0.137$, respectively).

Table 5 shows the PARP for AMI occurrence in the six groups calculated from the proportion of each group among the controls of this study and ORes obtained under adjustment for age and lifestyle shown in Table 4. In both men and women, the PARPs of the groups with disease histories were much higher than those without disease histories. The PARP of the normal physique group with disease histories showed the highest value among the six groups in both men (33.1%) and women (32.0%). The PARPs of the obese group with disease histories were 21.2% in men and 18.4% in women.

DISCUSSION

Although many studies have so far examined the strength of the effects of coronary risk factors and their combinations in Japan,[11-16] few have evaluated the effect of classical risk factors for the first AMI attack in terms of the degree to which it is modified by accompanying obesity.

Only in women, thinness was borderline significantly associated with an increased risk for AMI occurrence when we adjusted for the confounding effects of age, respective histories, and lifestyles (Table 3). This finding seems consistent with the results from a previous Japanese cohort study, which examined mortality,[17] though no studies have so far revealed the association of thinness with AMI in Western countries. Representative studies in the U.S.A. have demonstrated that obesity is a significant risk factor for AMI.[18] In the present study, obesity in women was also associated with the first AMI attack. However, in men, the positive association disappeared when adjusted for age, lifestyle and disease histories, while it was present when adjusted only for age and lifestyle. A Japanese cohort study showed that obesity was not significantly associated with an increased death from cardiovascular diseases when adjusted for risk factors such as hypertension, hyperlipidemia and diabetes mellitus.[19] In another Japanese study, although past obesity was associated with an increased risk of non-fatal AMI, the presence of obesity at the time of attack was not a risk factor.[20] Our results for men, which dealt with physique at the time of admission, are consistent with those of earlier studies.

Furthermore, consistent with previous studies, we found that all of the disease histories of hypertension, hyperlipidemia and diabetes mellitus were associated with an increased risk for AMI in both men and women.[21]

In men, although the presence of disease histories was significantly associated with AMI occurrence, obesity or thinness was not. The groups with at least one disease history were much more strongly associated with AMI occurrence than those with none, irrespective of physique. Therefore, it is suggested that the prevention of hypertension, hyperlipidemia or diabetes mellitus would be more urgent than the prevention of obesity or thinness in order to prevent AMI attacks in men. In the groups of women without disease histories, although obesity itself was significantly associated with AMI occurrence, thinness itself was not. The normal physique group with at least one disease history was 5.62 times more strongly associated with AMI occurrence than the normal physique group without disease histories. Moreover, it was found that the co-presence of thinness and disease history significantly elevated the risk for AMI attack (ORe: 15.24) above what might be expected as the product of their own risks ($1.54 \times 5.62 = 8.65$). This finding suggested that thinness and disease history interacted with each other to intensify their impact on AMI occurrence, while for obesity, no such relationship was observed. Rather, it was found that although the risk of the co-presence of obesity and disease history (ORe: 8.13) was higher than their own risks (ORe: 3.03, 5.62, respectively, Table 4), it was lower than what might be expected as the product of them ($3.03 \times 5.62 = 17.03$). In other words, as far as the subjects with disease histories were concerned, obesity and thinness, especially the latter, were more pronounced risk factors in women than in men.

Obesity is usually defined as BMI$\geqq$30.0 in Western countries. When we incidentally examined the association between obesity and AMI occurrence by applying this definition to our own study, the age-adjusted OR of obesity was found to be insignificant in both men and women (adjusted OR: men, 1.96; women, 1.63, $p > 0.1$). Furthermore, the proportion of obesity thus defined was 1.6~2.7% in our cases and controls, as against more than 30% in American subjects.[22] Therefore, it is only reasonable to suppose that if Japanese become as obese as Westerners in the future, then obesity may pose a serious risk factor for AMI attacks among them as well.

There was a difference in the distribution by age between cases and controls. The proportion

of older subjects, who were prone to be obese and to have disease histories, was smaller in controls than in cases in both men and women. This difference may not have been adjusted adequately when calculating ORs, thus causing an overestimation of the ORs of obesity and the presence of disease histories, though age was employed as an adjustment factor in the regression model. Despite such an overestimation, the PARP of the normal physique group with disease histories was higher than that of the obese group with disease histories. This difference in PARP was quite likely due to a much lower proportion of subjects belonging to the latter group than of those belonging to the former group, as shown in Table 5. These facts would indicate that a preventive strategy should be used for persons only if they had risk factor diseases, whether they are obese or not.

In Japan, health checkups for identifying people with metabolic syndrome will be introduced in 2008, and personalized health educational programs to improve lifestyles, i.e., intensive intervention, will be carried out. In that program, intervention for persons without visceral obesity is to be less intensive than for those with it. Strictly speaking, obesity and disease histories examined in the present study are not identical to the components of metabolic syndrome, since BMI rather than waist circumference was used to judge abdominal obesity, and the criteria for diseases examined in the present study may have been different from those newly proposed by the Japanese Society of Internal Medicine,[23] however, they are considered similar, qualitatively speaking. Therefore, persons with disease histories should be carefully treated irrespective of the presence or absence of obesity.

Although we calculated BMI using self-reported height and weight, previous studies have demonstrated that those two factors alone, and hence BMI based on them, were reliable and valid.[24,25]

We did not investigate the effects of gene polymorphism on AMI occurrence, but they have been reported in recent studies.[26,27] In the future, the relative importance of the effects of genotype and lifestyle should be clarified.

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