Relationship Between Serum High-Sensitivity C-Reactive Protein and Myocardial Infarction in a General Japanese Population

Teruyuki Sugiyama,¹ Shizukiyo Ishikawa,^{1*} Kazuhiko Kotani,^{1,2} Tadao Gotoh,³ Yoshihisa Itoh,⁴ Kazunori Kayaba,⁵ and Eiji Kajii¹

¹*Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University, Tochigi, Japan*

²*Department of Clinical Laboratory Medicine, Jichi Medical University, Tochigi, Japan*

³*Department of Internal Medicine, Shirotori National Health Insurance Hospital, Gifu, Japan*

⁴*Department of Laboratory Medicine, Eiju General Hospital, Tokyo, Japan*

⁵*School of Health and Social Services, Saitama Prefectural University, Saitama, Japan*

Background: Due to ethnic differences in its serum levels, clinical applicability of high-sensitivity C-reactive protein (hsCRP) to the primary prevention of atherosclerotic events has not completely been established in Japanese people whose hsCRP levels are lower than in Western people. This study investigated the relationship between hsCRP and myocardial infarction (MI) in general Japanese people. **Methods:** In relation to hsCRP, the incidence of MI was determined in a multiregional population-based prospective cohort study ($n = 6,637$; mean age 54.9 years; 2,513 men/4,124 women). **Results:** Fifty-six cases of MI were confirmed during a follow-up period of 10.7 years. The cut-

off levels of hsCRP between the highest quartile (fourth quartile) and the other quartiles combined were 0.368 mg/l in men and 0.279 mg/l in women. The hazard ratio (HR) of the highest quartile for MI was significantly greater than that of the other quartiles combined (multivariate-adjusted HR: 2.07, 95% confidence interval: 1.03–4.15) in men, but not in women (1.03, 0.35–2.21). **Conclusions:** In this population, serum hsCRP measurement predicted MI in men, but not in women. Under the low hsCRP level, a method of applicability of hsCRP to a risk assessment for preventing MI among Japanese people should be further explored. *J. Clin. Lab. Anal.* 30:999–1002, 2016. © 2016 Wiley Periodicals, Inc.

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A low-grade chronic inflammation is clinically reported to be associated with atherosclerotic pathology such as myocardial infarction (MI) (1–5). The primary prevention of MI is an issue worldwide for morbidity and mortality (6); therefore, a risk assessment of MI using laboratory markers remains to be explored. High-sensitivity C-reactive protein (hsCRP) has been identified as one of the most important markers among nontraditional risk factors (7), while serum CRP is used as an acute and nonspecific inflammatory protein in the daily practice (8).

In Japan, heart diseases including MI remain the second leading cause of mortality (9), even though the incidence of MI is lower in Japan than in Western countries (10, 11). As for serum hsCRP levels, ethnic differences

are well known (12) and clinical applicability of hsCRP measurement must be determined by its serum level of each ethnicity. We previously found that the CRP level was markedly lower in Japanese people than in Westerners

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*Correspondence to: Shizukiyo Ishikawa, Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-City, Tochigi 329-0498, Japan. E-mail: i-shizu@jichi.ac.jp

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(13). Then, a few studies using prospective cohort data reported serum CRP as a predictor of ischemic/coronary heart disease in Japanese people (14–16), while these studies were performed in a single region without a gender-separated analysis (14) or in a nested case–control design (15, 16). In contrast to the studies, the present prospective cohort study, the Jichi Medical School (JMS) Cohort Study, consisted of general Japanese residents in multiregional communities (17). Our understanding is that clinical applicability of hsCRP measurement to atherosclerotic events remains unestablished about in Japanese people. The relationship between hsCRP and MI was therefore investigated using the data of the JMS Cohort Study.

In the JMS Cohort Study, a multiregional population-based prospective cohort study, baseline data were obtained between April 1992 and July 1995 and followed the incidence of MI until the end of 2005 (11, 17). Serum hsCRP levels were measured in a total of 6,574 participants (2,479 men/4,095 women) in the present investigation. Inclusion criteria were adult residents who participated in the mass screening system held in the communities, while exclusion criteria were those who had a past history of MI at baseline. The study design and procedures were reviewed and approved by each municipal government and by the Ethics Committee at Jichi Medical School. Written informed consent was obtained individually.

The body mass index was measured based on height and weight in light clothing. Systolic and diastolic blood pressures were measured with an automated sphygmomanometer, which was placed on the right arms of the subjects with the appropriate cuff size after a seated position for 5 min at rest in accordance with the guidelines (18). Using questionnaires, the smoking status and past histories were asked. Serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, and blood glucose levels were measured enzymatically. Serum hsCRP levels were measured using highly sensitive nephelometry, a latex particle-enhanced immunoassay (NA Latex CRP Kit, Dade Behring, Tokyo, Japan). The hsCRP assay, which achieved an international standardization (19), was sufficiently sensitive to detect 0.030 mg/l of hsCRP. Undetectable hsCRP values were recorded as 0.015 mg/l.

Via yearly follow-up examinations, whether they had developed the first-ever MI was examined. Subjects who did not attend the follow-up examinations were contacted by mail or telephone. Those who had developed MI events during the study period were asked the hospital where the disease was diagnosed. Furthermore, the diagnoses were completed independently by a Diagnosis Committee, composed of a radiologist, neurologist, and two cardiologists. The diagnosis was based on the criteria of the World Health Organization MONICA Project (20).

The data were analyzed in each sex, and subjects were divided into quartiles according to hsCRP levels in each sex, respectively. We analyzed dichotomous categories for MI by hsCRP levels using the fourth quartile versus the first to third (combined) quartiles. Using Cox proportional hazard model, the hazard ratio (HR) and 95% confidence interval (CI) were calculated for the incidences of MI after adjustments for age and potential confounding factors (smoking status, body mass index, hypertension, hyperlipidemia, and diabetes mellitus). Significance was defined as $P < 0.05$. These analyses were done using IBM SPSS version 21.0 J.

As a result, the baseline characteristics of our study subjects are shown in Table 1. The median hsCRP levels were 0.16 mg/l in men and 0.09 mg/l in women. The total observation period was 71,050 person-years (26,528 person-years for men and 44,522 person-years for women). Fifty-six cases of MI (38 in men and 18 in women) were confirmed during the mean follow-up period of 10.7 years.

The group of the fourth quartile of hsCRP included 17 MI cases (crude incidence rate (CIR) = 0.26 per 1,000 person-years) and the group of the first to third (combined) quartiles included 21 MI cases (CIR = 0.11 per 1,000 person-years) in men. The group of the fourth quartile of hsCRP included seven MI cases (CIR = 0.07 per 1,000 person-years) and the group of the first to third (combined) quartiles included 11 MI cases (CIR = 0.03 per 1,000 person-years) in women. The HR of the fourth quartile of hsCRP for MI was significantly greater than the combined category of the first to third quartiles (age-adjusted HR: 2.06, 95% CI: 1.08–3.92; multiadjusted HR: 2.07, 95% CI: 1.03–4.15) in men, while no significant difference was detected in women (age-adjusted HR: 1.30, 95% CI: 0.50–3.39; multi-HR: 1.03, 95% CI: 0.35–2.21).

Thus, the present study showed serum hsCRP as a significant positive predictor for MI in men, but not in women, in general Japanese people. Given the nonspecific characteristic of CRP and the lower CRP level in Japanese people than in Westerners (13), the low hsCRP level generally leads to difficulties in deciding whether subjects are at high atherosclerotic risk. Under this situation, although the significant positive prediction of hsCRP for MI observed in the present study basically appears to be similar to previous studies (that had some differences in study designs and settings) (14–16), further confirmation of hsCRP as a predictor of the primary prevention of MI in a Japanese population would be valuable using a well-dedicated prospective cohort design in multiregional communities.

The predictive level of hsCRP for MI observed in our present study (approximately 0.3–0.4 mg/l) was lower more than that in previous studies, in which hsCRP levels <1, 1 to 3, and >3 mg/l denoted lower, average, and higher risks of cardiovascular events (this is not a case of

TABLE 1. Baseline Characteristics of Study Participants

	Total			hsCRP Q1: <0.039			hsCRP Q2: 0.039–0.159			hsCRP Q3: 0.160–0.367			hsCRP Q4: >0.368		
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD
Men															
Age (years)	2,513	54.9	13.3	628	53.0	13.2	623	53.3	13.6	632	55.2	13.1	630	58.0	12.6
hsCRP (mg/l)	2,513	1.01	4.53	628	0.02	0.01	623	0.09	0.04	632	0.24	0.06	630	3.69	8.51
		0.16 ^a													
Body mass index (kg/m ²)	2,357	22.8	2.9	588	22.1	2.4	584	22.6	2.6	600	23.1	2.9	585	23.3	3.3
Systolic blood pressure (mmHg)	2,366	129.4	21.1	591	124.9	19.3	588	129.2	20.5	597	130.7	21.2	590	132.6	22.7
Diastolic blood pressure (mmHg)	2,366	78.5	12.7	591	76.0	11.5	588	78.9	12.6	597	79.1	12.6	590	80.2	13.5
Glucose concentration (mg/dl)	2,502	103.0	27.2	628	102.0	23.8	621	104.1	33.7	630	102.3	23.8	623	103.5	26.5
Total cholesterol (mg/dl)	2,499	185.1	34.1	628	184.3	32.1	621	185.1	32.5	627	187.3	33.8	623	183.9	37.9
HDL cholesterol (mg/dl)	2,499	49.2	13.7	628	52.2	13.5	621	51.1	13.5	627	48.2	13.6	623	45.5	13.2
Triglycerides (mg/dl)	2,499	121.1	84.4	628	106.6	66.1	621	120.2	76.1	627	129.8	94.2	623	128.1	95.8
Smoking status															
Current smoker (%)	1,190	(50.5)		278	(47.1)		275	(46.8)		309	(52.4)		328	(55.6)	
Ex-smoker (%)	698	(29.6)		184	(31.2)		192	(32.7)		169	(28.6)		153	(25.9)	
Nonsmoker (%)	470	(19.9)		128	(21.7)		121	(20.6)		112	(19.0)		109	(18.5)	
Hypertension (%)	844	(33.6)		148	(23.6)		207	(32.2)		232	(36.7)		257	(40.8)	
Hyperlipidemia (%)	815	(32.4)		159	(25.3)		205	(32.9)		231	(36.6)		220	(34.9)	
Diabetes mellitus (%)	160	(6.4)		35	(5.6)		35	(5.6)		40	(6.3)		50	(7.9)	
Women															
Age (years)	4,124	54.9	12.6	1,185	52.6	12.5	870	53.5	12.8	1,037	55.4	12.3	1,032	58.3	11.9
hsCRP (mg/l)	4,124	0.63	2.97	1,185	0.02	0.00	870	0.05	0.01	1,037	0.18	0.05	1,032	2.29	5.61
		0.09 ^a													
Body mass index (kg/m ²)	3,941	22.9	3.1	1,128	21.9	2.7	838	22.4	2.8	992	23.4	3.1	983	23.9	3.5
Systolic blood pressure (mmHg)	3,982	126.2	21.8	1,141	120.9	20.2	840	123.7	21.1	1,009	128.8	22.0	992	131.8	22.4
Diastolic blood pressure (mmHg)	3,982	75.7	12.7	1,141	73.4	12.2	840	74.1	12.5	1,009	77.1	12.9	992	78.5	12.5
Glucose concentration (mg/dl)	4,108	97.4	19.9	1,181	95.1	16.9	865	96.7	16.9	1,033	98.3	20.8	1,029	99.7	23.6
Total cholesterol (mg/dl)	4,109	195.6	35.3	1,183	190.5	34.4	865	191.7	34.6	1,032	200.4	34.8	1,029	199.9	36.3
HDL cholesterol (mg/dl)	4,109	52.8	12.8	1,183	55.4	12.6	865	53.5	12.6	1,032	51.9	12.2	1,029	50.1	13.2
Triglycerides (mg/dl)	4,108	101.9	63.1	1,182	82.4	37.8	865	95.9	46.2	1,032	113.0	72.0	1,029	118.3	80.1
Smoking status															
Current smoker (%)	252	(6.4)		75	(6.7)		41	(4.9)		68	(6.8)		68	(7.0)	
Ex-smoker (%)	150	(3.8)		54	(4.8)		31	(3.7)		28	(2.8)		37	(3.8)	
Nonsmoker (%)	3527	(89.8)		992	(88.5)		762	(91.4)		900	(90.4)		873	(89.3)	
Hypertension (%)	1267	(30.7)		247	(20.8)		228	(26.2)		371	(35.8)		421	(40.8)	
Hyperlipidemia (%)	1345	(32.6)		272	(23.0)		240	(27.6)		404	(39.0)		429	(41.6)	
Diabetes mellitus (%)	137	(5.5)		23	(3.7)		22	(3.5)		39	(6.2)		53	(8.4)	

^aMedian of hsCRP.

Data are expressed as the mean and SD.

Japanese people) (1). Further, the level of hsCRP for MI in the present study seems to be lower than that for ischemic/coronary heart disease even in previous Japanese cohort studies; for example, approximately 1.0 (14), 0.85 (15), and 1.0 mg/l (16). This may have been partly due to our JMS cohort study including healthier Japanese participants from rural areas (17) as well as differences in the definitions of outcomes (i.e., sudden cardiac death was also defined as ischemic/coronary heart disease in previous studies (14, 16)).

We here indicated a predictive value of hsCRP for MI to be clearly seen in men, but not in women. This may be a hint of the applicability of hsCRP measurement. There can be a gender difference in the predictive value of hsCRP for MI because the greater significance of hsCRP for coronary heart disease in men than in women has been demonstrated in a previous Japanese study (15). The possible gender difference in the implication of hsCRP on MI in Japanese people merits further investigation.

The present study had the following strengths. The participants recruited were from multiregions, and a rigid followup was systemically performed. This has a contrast in that previous cohort studies, which examined the relationship between CRP and ischemic/coronary heart disease, were conducted in a single region or nested case-control design (14–16). This study had limitations. The number of subjects with MI was small. The incidence of MI is generally lower in Japan than in Western countries, particularly in women (9); thus, care must still be taken to an exact establishment of the significance of hsCRP on MI in women. More data by cohort studies with a longer followup and larger sample size that includes more women with incident MI are required.

In conclusion, the present study, the JMS cohort study, showed that serum hsCRP level was a significant positive predictor for MI in men, but not in women, in general Japanese people. Under the low hsCRP level, a method of clinical applicability of hsCRP measurement to a risk assessment for the primary prevention of MI among Japanese people should be further explored.

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