

Elevated C-Reactive Protein Is a Predictor of the Development of Diabetes in a General Japanese Population

The Hisayama Study

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OBJECTIVE — We examined the association between high-sensitivity C-reactive protein (CRP) levels and the development of diabetes in a general Japanese population.

RESEARCH DESIGN AND METHODS — A total of 1,759 Japanese subjects, aged 40–79 years and without diabetes (according to American Diabetes Association fasting criteria), were stratified into three groups according to CRP tertiles by sex and followed up prospectively for a mean of 9.0 years.

RESULTS — During the follow-up, 131 subjects (67 men and 64 women) developed diabetes. In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly as the tertiles of CRP levels increased. In multivariate analyses, the risk of developing diabetes was significantly higher in the highest CRP tertile than in the lowest after adjustment for a number of confounding factors (odds ratio 2.63 [95% CI 1.23–5.65] for men and 2.25 [1.01–5.01] for women). In stratified analyses, this CRP-diabetes association was stronger in subjects without obesity or other risk factors related to insulin resistance and in nondrinking subjects.

CONCLUSIONS — Our findings suggest that elevated CRP concentration is a significant predictor of diabetes in the general Japanese population, independent of obesity and insulin resistance.

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In some cohort and nested case-control studies in Western countries, an elevated C-reactive protein (CRP) level has been an independent predictor of diabetes (1–10). Recent cross-sectional studies have also demonstrated clear associations of elevated serum CRP levels with obesity and insulin resistance (11–13). These findings suggest that the inflammatory state illustrated by elevated CRP concentrations is associated with hyperglycemia and diabetes through obesity or increased insulin resistance. However, epidemiological findings concerning this

issue are still controversial; several studies have reported a significant positive association between elevation in CRP levels and the future risk of diabetes even after adjustment for BMI (1,2,4,7,9,10), whereas in other studies (3,6) this association disappeared after adjustment for BMI.

Japanese are characterized by low BMI levels and low CRP concentrations in blood compared with Westerners (14). Moreover, there have been no reports on the relationship between CRP levels and the development of diabetes among gen-

eral populations in Japan. The aim of the present study is to examine the effects of serum CRP levels on the development of diabetes in a prospective study of a defined Japanese population, taking into account comprehensive risk factors.

RESEARCH DESIGN AND METHODS

Study population and follow-up survey

In 1988, a screening survey for the present study was performed in the Town of Hisayama in Japan. A total of 2,587 residents aged 40–79 years (80.2% of the total population of this age-group) participated in the baseline survey. The diabetes classification was based on the fasting criteria of the American Diabetes Association (15), i.e., subjects with fasting plasma glucose levels ≥ 7.0 mmol/l or those who were taking diabetes medications were considered diabetic.

After the exclusion of 80 subjects who had already eaten breakfast before the examination, 233 subjects with diabetes, and 67 subjects whose CRP concentrations could not be measured due to insufficient quantities of stored sera, the remaining 2,207 subjects (926 men and 1,281 women) were enrolled in the baseline examination. Among those, 1,759 subjects (694 men and 1,065 women) underwent follow-up examinations in 1993–1998 (follow-up rate 79.7%). We considered a subject to have developed diabetes when he/she met the above-mentioned baseline criteria. During this period, 131 subjects (67 men and 64 women) developed diabetes.

Laboratory measurements

Plasma glucose levels were determined by a glucose-oxidase method, and serum insulin was measured by radioimmunoassay. HbA_{1c} levels were measured by high-pressure liquid chromatography. Total cholesterol, HDL cholesterol, and triglycerides were all determined enzymatically. Serum specimens collected at the time of CRP measurement were stored at -20°C until used in 2002. High-sensitivity CRP

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Abbreviations: CRP, C-reactive protein.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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concentrations were determined using a modification of the Behring latex-enhanced CRP assay. Sitting blood pressure was obtained three times and the average values used in the analyses. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current treatment with antihypertensive agents. BMI (kilograms per meters squared) was used as an indicator of obesity.

Diabetes in first- or second-degree relatives indicated a family history of diabetes. Those subjects engaging in sports at least three times a week during their leisure time comprised a regular exercise group. Information on smoking habits and alcohol intake was used to classify subjects as having current habits or not.

Statistical analysis

Because the distributions of CRP, fasting insulin, and triglycerides were skewed, these variables were natural log transformed for statistical analyses. To analyze CRP levels as categorical variables, these levels were divided into tertiles by sex (0.05–0.28, 0.29–0.77, and 0.78–13.5 mg/l for men and 0.05–0.24, 0.25–0.57, and 0.58–5.78 mg/l for women). The age-adjusted cumulative incidence of diabetes was calculated by the direct method and compared by the Mantel-Haenszel χ^2 test using 10-year age-groupings. Age- and multivariate-adjusted odds ratios (ORs) and 95% CIs were calculated by logistic regression analysis. $P < 0.05$ was considered statistically significant in all analyses.

This study was conducted with the approval of the Ethics Committee of

Table 1—Characteristics of subjects by sex

	Men	Women
n	694	1,065
Age (years)	58 \pm 10	57 \pm 10
High-sensitivity CRP (mg/l)	0.49 (0.07–7.14)	0.36 (0.06–3.22)
Fasting plasma glucose (mmol/l)	5.6 \pm 0.5	5.5 \pm 0.5
HbA _{1c} (%)	5.5 \pm 0.5	5.4 \pm 0.5
Family history of diabetes (%)	9.3	7.3
Fasting insulin (pmol/l)	30.0 (18.0–72.0)	36.0 (18.0–72.0)
BMI (kg/m ²)	22.9 \pm 2.9	23.0 \pm 3.1
Total cholesterol (mmol/l)	5.10 \pm 1.04	5.57 \pm 1.05
HDL cholesterol (mmol/l)	1.26 \pm 0.30	1.35 \pm 0.29
Triglycerides (mmol/l)	1.25 (0.58–3.49)	1.02 (0.49–2.33)
Systolic blood pressure (mmHg)	131 \pm 19	130 \pm 20
Diastolic blood pressure (mmHg)	80 \pm 11	75 \pm 11
Hypertension (%)	41.5	32.7
Current drinking (%)	61.0	8.5
Current smoking (%)	47.6	5.4
Regular exercise (%)	16.1	4.9

Data are means \pm SD or medians (95% CI) unless otherwise indicated.

Kyushu University, and written informed consent was obtained from all participants.

RESULTS— The clinical characteristics of the subjects by sex are shown in Table 1. The mean age was 58 years for men and 57 years for women.

In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly with elevating tertiles of baseline serum CRP concentrations. The incidences in the 3rd tertile for both sexes and in the 2nd tertile for men were significantly higher than in the 1st tertile (Fig. 1). As shown in Table 2, the risk of future diabetes in either sex was more than threefold higher in the 3rd tertile than in the 1st tertile after adjustment for age. These associations remained substantially

unchanged even after adjustment for the other confounding factors, including age, family history of diabetes, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, current drinking, current smoking, and physical activity (adjusted OR 2.63 [95% CI 1.23–5.65], $P = 0.014$, for men and 2.25 [1.01–5.01], $P = 0.049$, for women).

We next estimated the age- and sex-adjusted ORs and 95% CIs for the development of diabetes by an increment of 1 log CRP in men and women together according to the other risk factor levels (Table 3). Analyses were performed by dividing the subjects into three groups according to tertiles of BMI, triglycerides, and HDL cholesterol levels or into two

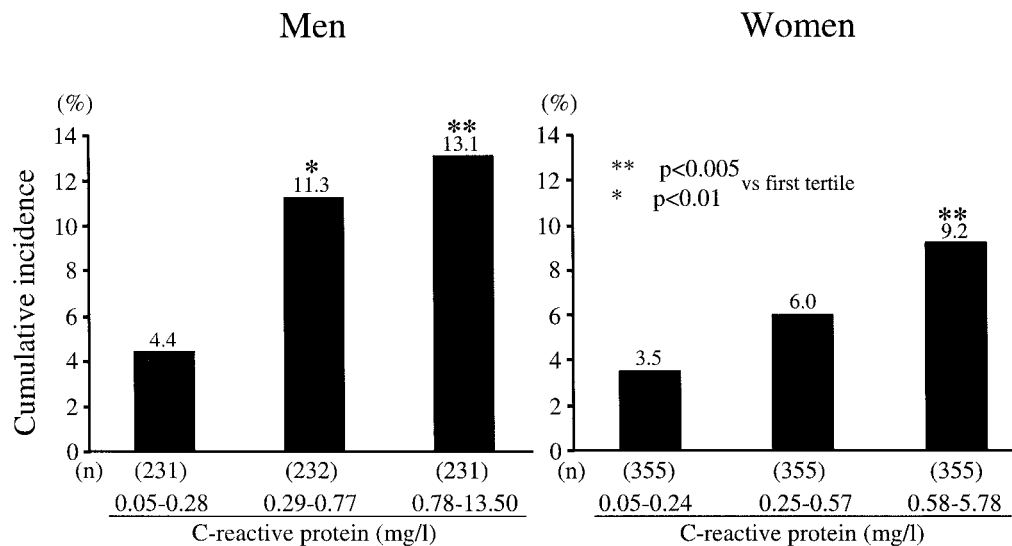


Figure 1—Age-adjusted cumulative incidence of diabetes according to tertiles of serum high-sensitivity CRP levels by sex.

Table 2—Age- or multivariate-adjusted ORs and 95% CIs for occurrence of diabetes according to tertiles of serum high-sensitivity CRP levels by sex

	High-sensitivity CRP level (mg/l)								
	Men				P for trend	Women			P for trend
	0.05–0.28	0.29–0.77	0.78–13.50			0.05–0.24	0.25–0.57	0.58–5.78	
Population at risk (n)	231	232	231		355	355	355		
Cases of diabetes (n)	11	26	30		10	21	33		
Age-adjusted OR (95% CI)	1 (referent)	2.67 (1.28–5.56)	3.23 (1.57–6.70)	0.002	1 (referent)	2.12 (0.98–4.58)	3.35 (1.60–7.03)	0.001	
Multivariate-adjusted OR (95% CI)	1 (referent)	1.96 (0.92–4.19)	2.63 (1.23–5.65)	0.014	1 (referent)	1.76 (0.80–3.87)	2.25 (1.01–5.01)	0.049	

Multivariate adjustment was made for age, family history of diabetes, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, current drinking, current smoking, and physical activity.

groups by hypertension status, current drinking, and current smoking. Significant positive associations between CRP levels and incident diabetes were observed among subjects in the 1st tertile of BMI, among subjects in the 1st and 2nd tertiles of triglycerides, among subjects of the 2nd and 3rd tertiles of HDL cholesterol, and among subjects without hypertension or current drinking. Significant associations were also observed in both smokers and nonsmokers. However, clear CRP-diabetes associations were not seen in the other categories of any risk factors.

CONCLUSIONS— We demonstrated in a prospective study of a general Japanese population that elevated CRP level is an independent predictor of diabetes for both sexes even after adjustment for comprehensive risk factors. In stratified analyses, the CRP-diabetes association was stronger in subjects without risk factors related to insulin resistance, such as obesity, dyslipidemia, and hypertension, and among nondrinkers, whereas the presence of a current smoking habit did not affect this association.

To our knowledge, this is the first report to indicate that the low-grade inflammatory state illustrated by increased CRP is an independent risk factor for developing diabetes in a general Japanese population. Similar findings were observed in a Japanese-American population (13) as well as in some other Western populations (5–12,14). Since Japanese Americans have a Western lifestyle, their findings cannot be generalized to Japanese living in Japan. Our subjects were thinner than those in previous reports (1–10). Our findings suggest that the subclinical inflammatory process has an important role in the development of di-

abetes in relatively lean Asian populations, as it does in Western populations.

Recent cross-sectional epidemiological data have demonstrated that elevated serum CRP levels are associated with obesity, insulin resistance, and glucose intolerance (11–13). These findings suggest that the inflammatory state affects glucose levels in blood and increases the risk of diabetes via obesity or insulin resistance. However, our study showed that the association between CRP levels and the development of diabetes is independent of serum insulin levels as well as BMI. These findings are in accord with those of sev-

eral other cohort studies (1,9). Additionally, our stratified analyses showed that the CRP-diabetes association was stronger particularly in individuals with low levels of risk factors related to insulin resistance. Therefore, a low-grade inflammatory state can be considered a risk factor for diabetes independent of obesity and insulin resistance, and unknown mediators are also thought to be involved in the development of diabetes.

In our subjects, the influence of CRP on the incidence of diabetes was stronger in nondrinkers than in drinkers. Some studies have shown that moderate alcohol

Table 3—Age- and sex-adjusted ORs and 95% CIs for occurrence of diabetes by an increment of 1 log high-sensitivity CRP in all subjects according to risk-factor levels

Risk factor	Population at risk (n)	Cases of diabetes (n)	Age- and sex-adjusted OR (95% CI)	P
BMI (kg/m ²)				
≤21.5	586	29	1.36 (1.05–1.75)	0.017
21.6–24.2	587	35	1.20 (0.92–1.57)	NS
≥24.3	586	67	1.25 (0.99–1.59)	NS
Triglycerides (mmol/l)				
≤0.88	587	30	1.30 (1.01–1.67)	0.042
0.89–1.34	582	29	1.50 (1.12–2.01)	0.007
≥1.35	590	72	1.16 (0.94–1.43)	NS
HDL cholesterol (mmol/l)				
≤1.14	572	49	1.04 (0.82–1.31)	NS
1.15–1.40	583	44	1.43 (1.13–1.81)	0.003
≥1.41	604	38	1.57 (1.20–2.07)	0.001
Hypertension				
Without	1,123	54	1.45 (1.18–1.77)	0.0003
With	636	77	1.16 (0.95–1.41)	NS
Current drinking				
Without	1,246	77	1.43 (1.20–1.71)	0.0001
With	513	54	1.14 (0.92–1.42)	NS
Current smoking				
Without	1,372	95	1.29 (1.09–1.53)	0.003
With	387	36	1.34 (1.04–1.72)	0.022

consumption is associated with lower CRP concentrations (16,17). Additionally, recent cohort studies have revealed that moderate alcohol consumption reduced the risk of future type 2 diabetes (18,19). Therefore, the intake of alcohol may attenuate the influence of CRP on the development of diabetes.

A recent cohort study has reported a significant association between inflammation and future diabetes among non-smokers but not among smokers (8). In our subjects, however, an association between elevated CRP levels and incident diabetes was observed in both nonsmokers and smokers. This suggests that the CRP-diabetes association is independent of current smoking.

Several limitations of our study should be discussed. The primary limitation is that a diagnosis of diabetes was not based on a 75-g oral glucose tolerance test, but on a single reading of fasting glucose level, as was the case in other epidemiological studies (2,8,9). Subjects with diabetes having normal fasting glucose levels were misdiagnosed in our study. Additionally, some of the participants who were classified as having worsening fasting glucose status may not have been so categorized after repeated testing. These misclassifications should weaken the association found in this study. Therefore, the true association may be stronger than that shown in our findings. A secondary limitation is that CRP concentrations were measured in serum conserved for a long period at -20°C . However, the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years was confirmed in the Reykjavik Study (20). The last limitation is that our study lacked information on drug use, which could affect serum CRP levels. It is known that several medications can alter CRP levels, including statins, ACE inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone (21). However, these medications were rarely used in our country in 1988. This suggests that such a bias does not invalidate the present findings.

In conclusion, we showed that subclinical elevation in CRP concentrations is an independent predictor of diabetes in a general Japanese population. CRP was an effective predictor of diabetes in individuals with the lowest BMI as well as in individuals without other risk factors related to insulin resistance. These findings add to the notion that low-grade in-

flammation is an important factor in the pathogenesis of type 2 diabetes. Further study is necessary to clarify the role of inflammation in the cascade to the development of diabetes.

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