〈Original Article〉

Epidemiological study of the relationship between C-reactive protein and diabetes in Japanese females

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Summary Recent evidence suggests that a small percentage of chronic inflammations are associated with the onset of diabetes. Based on this association, C-reactive protein (CRP), an inflammatory marker, has been garnering attention as a new risk factor for diabetes. However, according to reports from a large-scale epidemiological study conducted in the US and Europe, no conclusive evidence was found linking CRP levels and diabetes. Therefore, we conducted an epidemiological study of Japanese females from Habikino City during routine medical examinations and found through cross-sectional and longitudinal analysis that CRP levels and diabetes are indeed linked in these women.

Key words: C-Reactive Protein (CRP), A1C, Diabetes, Medical examination.

1. Introduction

The growing number of people affected by diabetes is a worldwide concern. In November 2011, the International Diabetes Federation (IDF) published the Volume 5 of the Diabetes Atlas, which estimated that 366 million adults between the ages 20-79 years were affected with diabetes, a figure that is expected to rise to 552 million by 2030[1]. Japan is the sixth-most affected country in the world with 10.67 million diabetic adults. Considering this situation, early detection of diabetes is exceedingly important for increasing the healthy lifespan of Japanese citizens.

A mechanistic understanding of the onset of diabetes and its mode of affecting a patient has not been completely elucidated. However, clinical and epidemiological studies have reported that age, obesity, high blood pressure, abnormal glucose tolerance, and insulin resistance are all risk factors for diabetes[2-10]. Furthermore, an association between chronic inflammation and onset of diabetes has been recently reported[11, 12] and the levels of the inflammatory marker C-reactive protein (CRP) has been suggested as a risk factor for diabetes. Interestingly, large-scale clinical studies conducted in the US and Europe did not find any conclusive evidence linking CRP levels and diabetes[13-15]. Moreover, CRP levels vary depending on ethnic group and sex, which can affect

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the risk of onset of diabetes[16].

Relatively few Japanese studies with healthy adults have been conducted regarding the relationship between CRP levels and diabetes, compared to the US or European countries. Data from a large-scale clinical study centered on the Japanese population are required to determine the validity and effectiveness of using CRP levels as a risk factor for the onset of diabetes. Here, we report the results of an epidemiological study of Japanese females from Habikino City during routine medical examinations to study the relationship between CRP levels and the onset of diabetes.

2. Subjects and Methods

Our CRP reference values for the Japanese population were obtained from the findings of Nakamura et al.[17]. The normal value was set to 0.2 mg/dl; the study population was divided into 2 target groups: a low CRP cohort (measured CRP less than 0.2 mg/dl) and a high CRP cohort (measured CRP more than 0.2 mg/dl). The values for glycated hemoglobin (HbA1c) were converted to corresponding values by the National Glycohemoglobin Standardization Program (NGSP) using the guidelines and basic policies for international standardization[18] these values are referred to as A1C. We classified subjects with an A1C value above 6.5% as diabetic, according to the diagnostic criteria set by the American Diabetes Association (ADA).

1. Cross-sectional study

Of the 7,105 female participants from Habikino City who underwent a standard medical examination in the year 2000, 6,729 were selected (average age, 60.3 ± 10.5 years) on the basis of completeness of measured variables for CRP, body mass index (BMI), systolic/diastolic blood pressure, total cholesterol, triglycerides, HbA1c, and drinking and smoking habits. Further, 376 of the 7,105 were excluded from the study because their CRP levels were above 1.0 mg/dl, which is indicative of systemic inflammatory disease. We performed a multiple regression analysis using A1C as the target variable and age, BMI, blood pressure, total cholesterol, triglycerides, CRP, and drinking and smoking history as the dependent variables. We set the ratio of onset of diabetes for the low CRP cohort to 1 and calculated the adjusted odds ratio (OR) and that for confidence interval (CI) for conciseness when representing the data in the results section. (adjusted factors: age, BMI, and total cholesterol) for the high CRP cohort using logistic regression analysis.

2. Longitudinal study

We selected 2,164 non-diabetic participants who had complete records of the measured variables for the period between 2001 and 2005 and whose CRP values were below 1.0 mg/dl. The participants were grouped into the low CRP or high CRP cohorts, depending on the CRP values measured in the year 2000. Using the Kaplan-Meier estimation, we calculated the cumulative rate of incidence of diabetes during the 5-year follow-up period from 2000. Adjusted OR were calculated for the high CRP cohort (adjusted factors: age, BMI, and total cholesterol) for each year of the 5-year periods (2000-2001, 2000-2002, 2000-2003, 2000-2004, and 2000-2005), and the onset of diabetes for the low CRP cohort was set to 1. Additionally, we monitored changes in CRP levels for each participant that developed diabetes during the study period in both cohorts. All statistical analyses were performed using IBM SPSS version 19.0 for Windows, with a significance level of 5%.

The protocol of this study was approved by the Institutional Review Board of Osaka Prefecture University. All data were collected by health center of Habikino City, which allowed Osaka Prefecture University to use these data for analysis.

3. Results

1. Cross-sectional study

Table 1 shows the baseline characteristics of both low and high CRP cohorts. A significantly higher A1C value was observed for the high CRP cohort (5.4 ± 2.6%) than the low CRP cohort (5.1 ± 1.4%) ($p < 0.001$). Multiple regression analysis using A1C as the objective variable is shown in Table 2. An

independent positive correlation was observed between CRP levels and A1C. Furthermore, the same positive correlation was observed between A1C and age, BMI, and total cholesterol. The adjusted OR for the onset of diabetes was significantly higher for the high CRP cohort (2,164; 95% CI, 1.194-1.893) than the low

Table 1 Characteristics of participants based on C-reactive protein (CRP) levels

Variables	Low CRP (n=5,312)		High CRP (n=1,417)		*P*-value
	Mean	SD	Mean	SD	
Age (y)	59.8	10.3	62.2	10.4	＜0.001
BMI (kg/m^2)	22.7	3.0	24.0	3.6	＜0.001
Systolic BP (mmHg)	129.3	18.6	133.0	18.1	0.312
Diastolic BP (mmHg)	76.4	10.8	77.6	10.6	0.342
Total-Choresterol (mg/dl)	213.3	33.1	216.9	34.5	0.016
HDL-Choresterol (mg/dl)	64.5	14.9	60.0	14.8	0.822
Triglyceride (mg/dl)	114.2	59.7	134.4	71.5	＜0.001
A1C (%)	5.1	1.4	5.4	2.6	＜0.001
Current smoking (%)	4.1	－	5.4	－	0.052
Current drinking (%)	10.7	－	8.0	－	0.003

SD: Standard Deviation. BMI: Body Mass Index. BP: Blood Pressure.
HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein

Table 2 Multiple regression analysis using A1C as the objective variable

Explanatory Variables	A1C (Objective variable)			*P*-value
	Regression Coefficient	SE	95% CI	
Age	0.007	0.002	0.003 － 0.012	0.002
BMI	0.029	0.008	0.014 － 0.044	＜0.001
Systolic BP	0.002	0.002	-0.002 － 0.005	0.297
Diastolic BP	-0.002	0.003	-0.008 － 0.004	0.457
Total-Choresterol	0.003	0.001	0.001 － 0.004	0.001
HDL-Choresterol	-0.002	0.002	-0.006 － 0.001	0.191
Triglyceride	0.001	0.001	-0.001 － 0.002	0.124
C-Reactive Protein	0.538	0.177	0.191 － 0.885	0.002
Current smoking	-0.067	0.077	-0.217 － 0.084	0.385
Current drinking	-0.029	0.113	-0.250 － 0.191	0.793

SE: Standard Error. BMI: Body Mass Index. BP: Blood Pressure.
HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein

Table 3 Adjusted odds ratio for onset of diabetes based on C-reactive protein (CRP)

Follow up	Crude OR				Multiple adjusted OR*			
	Low CRP (n = 1,748)	High CRP (n = 416)	95%CI	*P*-value	Low CRP (n = 1,748)	High CRP (n = 416)	95%CI	*P*-value
2000-2001	1.00	2.53	1.54 － 4.34	＜0.005	1.00	2.13	1.24 － 3.64	0.006
2000-2002	1.00	1.83	1.22 － 2.74	0.003	1.00	1.46	0.96 － 2.21	0.077
2000-2003	1.00	2.04	1.44 － 2.87	＜0.001	1.00	1.56	1.09 － 2.23	0.015
2000-2004	1.00	1.93	1.40 － 2.66	＜0.001	1.00	1.50	1.07 － 2.09	0.018
2000-2005	1.00	1.86	1.37 － 2.54	＜0.001	1.00	1.43	1.03 － 1.98	0.031

*Adjusted for Age, BMI, Total Choesterol
OR: Odds Ratio. CI: Confidence Interval.

CRP cohort (adjusted OR, 1.00; $p < 0.001$).

2. Longitudinal study

During the follow-up period, 223 participants developed diabetes. The cumulative rate of incidence for the high CRP cohort (18.5%) was significantly higher than that for the low CRP cohort (9.9%) (Fig. 1). Moreover, when the adjusted OR for the onset of diabetes for the low CRP cohort was set to 1, the adjusted OR for each year of the 5-year period for the high CRP cohort were 2.212 (95% CI, 1.240-3.640; 2000-2001), 1.456 (95% CI, 0.961-2.208; 2000-2002), 1.557 (95% CI, 1.090-2.225; 2000-2003), 1.497 (95% CI, 1.072-2.090; 2000-2004), and 1.429 (95% CI, 1.033-1.977; 2000-2005) (Table 3). Average CRP levels in the low CRP cohort rose continuously leading

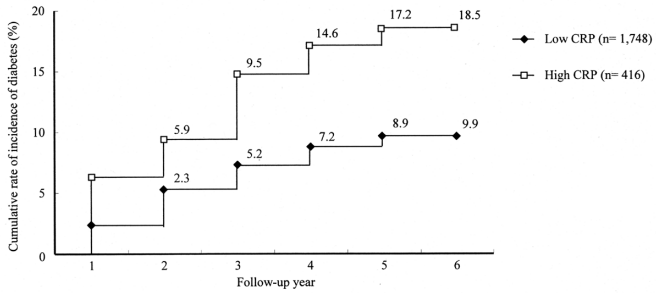

Fig. 1 Kaplan-Meyer curve of cumulative incidence of diabetes during follow-up.

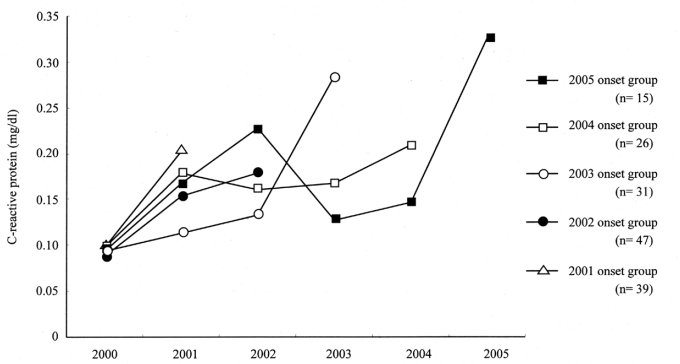

Fig. 2 Changes in the C-reactive protein (CRP) Levels in the low CRP cohort until the onset of diabetes.

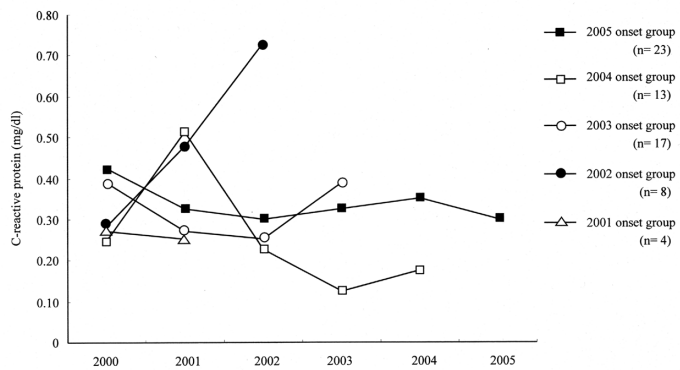

Fig. 3 Changes in the C-reactive protein (CRP) levels in the high CRP cohort until the onset of diabetes.

up to the year of onset of diabetes and reached its peak value during that year (Fig. 2). On the other hand, CRP levels for the high CRP cohort were stable above 0.2 mg/dl for most of the study period (Fig. 3).

4. Discussion

Based on the data above, a significant association between CRP cohorts and unadjusted rates of incidence of diabetes was observed in Japanese female adults from Habikino City surveyed in 2000, suggesting that CRP levels and the onset of diabetes are correlated. A significant correlation was also observed using the predictive power of the logistic regression model, adjusted for age, BMI, and total cholesterol. This suggests that CRP levels can be used as an independent risk factor to predict the onset of diabetes, similar to its use in other large-scale epidemiological studies conducted in Japan[19, 20]. Considering that 9.9% of participants in the low CRP cohort developed diabetes within 5 years of the study and that their CRP levels rose as they neared the onset of diabetes, monitoring CRP levels with age can be an important aspect of mitigating the onset of diabetes.

Studies have shown that CRP levels are higher among subjects with diabetes than among those without; even among unaffected people, a high A1C level is correlated with high CRP levels[21, 22]. Furthermore, Festa et al.[23] showed that an independent interrelationship exists between CRP levels and insulin resistance. In addition, high blood glucose is known to accelerate chronic inflammation[24, 25]. These studies confirm our results regarding the relationship between rising CRP levels and the onset of diabetes.

Although our study did not analyze highsensitive CRP values, a relationship between conventional CRP levels and diabetes was observed, similar to that reported by King et al.[26] We believe that monitoring conventional CRP levels and A1C during routine examinations can lead to early diagnosis of diabetes.

5. Conclusions

CRP levels were associated with the onset of diabetes in Japanese female adults. Even a clinically non-relevant CRP level (0.2-0.3 mg/dl) can be a risk factor for diabetes; therefore, we believe that careful monitoring of both CRP and A1C levels with aging can lead to early detection of diabetes.

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