

Elevated C-Reactive Protein Is a Risk Factor for the Development of Type 2 Diabetes in Japanese Americans

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OBJECTIVE — Increasing evidence from a cohort of Caucasians recently suggests that an elevated level of C-reactive protein (CRP) is associated with an increased risk of developing type 2 diabetes. However, Japanese subjects are skewed to lower CRP concentrations than westerners. Therefore, the effect of CRP on the development of type 2 diabetes among Japanese is unclear.

RESEARCH DESIGN AND METHODS — We examined 396 male and 551 female nondiabetic Japanese Americans who underwent a 75-g oral glucose tolerance test (GTT) and were then followed for an average of 6.5 years. We investigated whether elevated serum CRP level is a risk factor in the development of type 2 diabetes among these subjects.

RESULTS — Subjects with a high CRP level showed a significantly higher incidence of type 2 diabetes compared with subjects with a low level among both men ($P = 0.028$) and women ($P = 0.004$) in a log-rank test. In a Cox proportional hazards model dividing quartiles of CRP, the hazard ratios for diabetes development in the highest versus lowest quartile of CRP levels were 2.84 (95% CI 1.09–7.39) among men and 3.11 (1.25–7.75) among women after adjustment for age, smoking, family history of diabetes, classification of a 75-g GTT, hormone replacement therapy (among women), BMI, and homeostasis model assessment.

CONCLUSIONS — Among Japanese Americans, CRP may be a risk factor for development of type 2 diabetes independent of either obesity or insulin resistance. Our results suggest that inflammation may be closely related to the mechanism of type 2 diabetes among Japanese Americans.

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Complications of diabetes reduce patients' quality of life. Therefore, it is necessary to identify individuals with glucose intolerance as early as possible to prevent its progression into diabetes. Thus, it may be more efficient to intervene when high-risk factors in subjects can be readily identified.

C-reactive protein (CRP) is a marker of acute inflammation and is generally used as a measure of inflammatory dis-

ease. Recently, CRP increases have been reported in obesity (1,2) and type 2 diabetes (1). Thus, there is increasing evidence to suggest that insulin resistance is a chronic low-grade inflammatory state (3). In prospective case-control studies (4–9), elevated levels of CRP predict the development of type 2 diabetes, supporting a possible role for inflammation in diabetogenesis (4, 6–8).

According to the literature on Japa-

nese populations (10), Japanese subjects are skewed to lower CRP concentrations than westerners. Therefore, the acute-phase response may vary due to racial differences. However, there have been no published reports investigating the relationship between CRP and the development of type 2 diabetes among Japanese.

Although Americans of Japanese descent share a virtually identical genetic makeup with native Japanese currently living in Japan, Japanese Americans have approximately twice the incidence of type 2 diabetes compared with Japanese living in Japan, primarily because of a westernized lifestyle (11). We compared those groups that developed diabetes during the long follow-up period with those that did not develop the disease to investigate the role of CRP in diabetes in men and women.

RESEARCH DESIGN AND METHODS

Study subjects were Japanese Americans enrolled in medical surveys conducted from 1988 to 2000 in Hawaii and Los Angeles, California. Subjects were free of infectious symptoms, autoimmune disease, or any other acute conditions as assessed by medical interview. The surveys have been previously described in detail elsewhere (11–13). The study population consisted of 396 men and 551 women who did not have diabetes, as ascertained by a 75-g glucose tolerance test (GTT) at baseline. Among all repeating participants, 43.6% were examined twice, 24.2% three times, 17.3% four times, 14.8% five times, and 0.1% six times. Family history (FH) of type 2 diabetes, use of hormone replacement therapy (HRT) for women, and smoking status were assessed using standard interviewing procedures. The relationship between CRP and the development of diabetes during the follow-up period was analyzed. During each follow-up examination, participants who were free of diabetes at baseline had a 75-g GTT performed after an overnight fast. Incident diabetes was diagnosed as fasting glucose of ≥ 7 mmol/l or 2-h glucose of

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Abbreviations: CRP, C-reactive protein; FH, family history; GTT, glucose tolerance test; HOMA, homeostasis model assessment; HRT, hormone replacement therapy.

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

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≥ 11.1 mmol/l (14). Blood was centrifuged, and the obtained serum was immediately frozen at -80°C . Serum samples were subsequently brought back to Japan. Insulin was measured by double-antibody radioimmunoassay. CRP was measured using latex-enhanced immunonephelometric assays (15) on a BNII analyzer (Dade Behring, Tokyo, Japan). Insulin resistance was evaluated with homeostasis model assessment (HOMA) (16). This study was approved by the ethics committee of the Hiroshima University and the Council of the Hiroshima Kenjin-Kai Association in Hawaii and Los Angeles.

In this study, data on men and women aged 20–93 years were analyzed independently. Results were expressed as the means \pm SEM. Because triglycerides, HOMA, and BMI did not show normal distributions, the data were analyzed after logarithmic transformation. Baseline CRP concentration was divided at the 50th percentile of the sex-specific distributions (>0.68 mg/l for men and >0.76 mg/l for women), and relationships between CRP and the development of diabetes were evaluated using Kaplan-Meier plots and log-rank tests. To test the significance of CRP as a predictor of incidence of type 2 diabetes, CRP concentration was divided into quartiles based on its population (among men, <0.39 , 0.39 – 0.67 , 0.68 – 1.43 , and ≥ 1.44 mg/l; among women, <0.37 , 0.37 – 0.75 , 0.76 – 1.66 , and ≥ 1.67 mg/l); quartile specific hazard ratios were estimated through a Cox proportional hazards model. The numbers of the subjects were 99, 98, 99, and 100, respectively, among men; the numbers were 138, 138, 137, and 138, respectively, among women. The development of diabetes was designated the dependent variable (1, developed diabetes; 0, did not develop diabetes), whereas age, smoking status, FH (1, positive; 0, negative), classification of a 75-g GTT (1, impaired glucose tolerance; 0, normal glucose tolerance), HRT for women, BMI, and HOMA were used as independent variables in addition to CRP quartiles. For proportional hazards, assumption was checked with a graphical plot of $\log S_t$ versus $\log t$ for the variables included in the model (S denoted the survival function, and t denoted time) and found to be acceptable. For all analyses, SAS package version 8.2 (SAS, Cary, NC) was used.

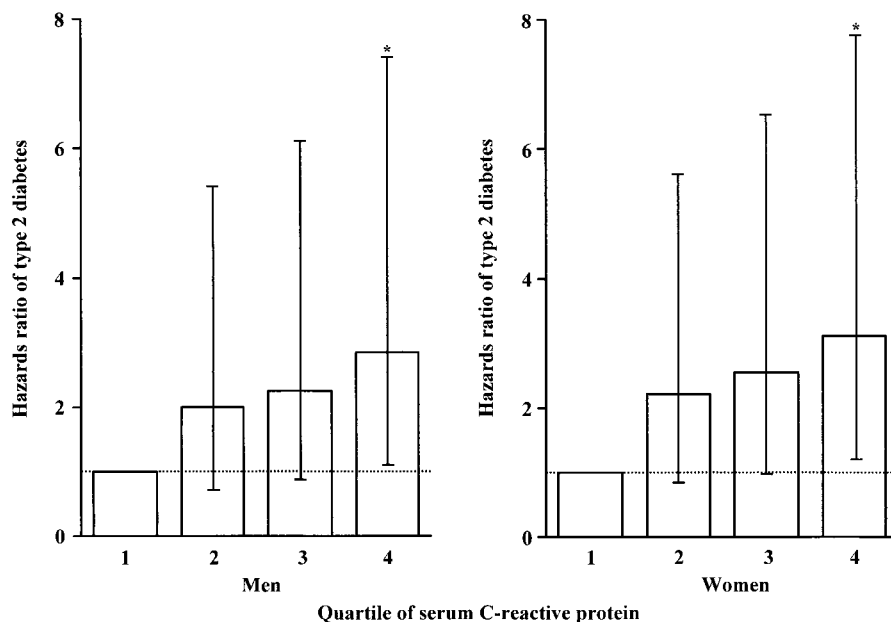


Figure 1—Adjusted hazard ratio of type 2 diabetes from a Cox proportional hazards model according to baseline serum CRP concentrations. Data were expressed after adjustment of age, smoking status, FH, classification of 75-g GTT, HRT use for women, BMI, and HOMA. Error bars indicate 95% CI. Trend analysis was $P = 0.035$ among men and $P = 0.036$ among women. * $P < 0.05$ compared with the lowest quartile of each sex.

RESULTS— In this study, the distribution of serum CRP was skewed to low levels. A total of 57 of 396 men and 65 of 551 women developed diabetes during the follow-up period (6.54 ± 0.10 years). We subsequently investigated the rate of development of the disease according to dichotomized CRP levels. Among men with a high CRP level, 36 of 199 were diagnosed with type 2 diabetes. Among men with a low CRP level, 21 of 197 were diagnosed with the disease. Among women with a high CRP level, 43 of 275 were diagnosed with type 2 diabetes. Among women with a low CRP level, 22 of 276 were diagnosed with the disease. We observed significant differences in rates of incidence between subjects with a high versus low CRP level in both sexes because Kaplan-Meier curves and log-rank tests ($P = 0.028$ for men; $P = 0.004$ for women) were statistically significant.

In a Cox proportional hazards model including quartiles of CRP, the hazard ratios for developing diabetes by increasing quartiles of CRP were 1.0, 1.99 (95% CI 0.73–5.41), 2.24 (0.83–6.03), and 2.84 (1.09–7.39) among men, respectively ($P = 0.035$ for trend), and the hazard ratios for increasing quartiles of CRP were 1.0, 2.22 (0.86–5.74), 2.55 (1.00–6.49), and 3.11 (1.25–7.75) among women, re-

spectively ($P = 0.036$ for trend) adjusted for age, smoking status, FH, classification of a 75-g GTT, HRT for women, BMI, and HOMA (Fig. 1). The adjusted hazard ratio per unit of CRP was 1.00 (1.00–1.001) among all participants, with the same ratio observed among both men and women. The adjusted hazard ratios per unit log (CRP) were 1.22 (1.03–1.45) among all participants, 1.14 (0.89–1.45) among men, and 1.40 (1.09–1.80) among women.

CONCLUSIONS— Although the influence of CRP on the development of type 2 diabetes in Japanese populations has not been demonstrated, this study did show that a relationship exists between CRP and the development of type 2 diabetes in Japanese Americans, as well as other races (4,6–8), which is a population thought to be genetically identical to native Japanese populations.

CRP levels followed in this study have been shown to be the same (2,17) or lower (1,4,7,9,18) in Japanese-Americans compared with Caucasians. However, they were elevated compared with those of native Japanese populations (10,19). From an early age, Japanese Americans have lived in a highly westernized environment, with features such as a high-fat

diet, for a longer period of time and more intensely when compared with native Japanese (12), resulting in greater insulin resistance. Elevated proinflammatory mediators, such as tumor necrosis factor- α , subsequent to exposure to a high-fat diet (20) might result in a low-grade inflammatory state (21). This might be one explanation of the relationship between CRP and the westernized lifestyle among Japanese Americans.

CRP is thought to be produced in the liver (2) and stimulated by tumor necrosis factor- α , which is itself derived from adipose tissue (22) and predominantly induced by interleukin-6 (23). Accordingly, the possibility exists that CRP is an indirect indicator of insulin resistance via obesity. In this study, the high CRP group manifested the characteristic so-called metabolic syndrome, which is namely a tendency toward elevated blood glucose, insulin, BMI, and triglycerides and decreased HDL cholesterol levels (data not shown). However, in both sexes, the highest quartile group was at significantly higher risk for developing diabetes compared with the lowest quartile group after adjustment for BMI and HOMA. Additionally, the hazard proportion trend was observed as quartiles increased (Fig. 1). Therefore, the low-grade inflammatory state illustrated by CRP increase was considered a risk factor independent of obesity or insulin resistance, which might suggest an unknown mediator involved in the development of diabetes.

The mechanisms of correlation between CRP and the development of diabetes are unclear. However, there are several possible explanations. One of them is the oxidative stress generated hyperglycemia (24). Oxidative stress might be implicated in promoting a state of low-grade inflammation indicated by markers such as CRP with elderly type 2 diabetes (25). On the other hand, oxidative stress was thought to impair insulin endocytosis in endothelial cell lines (26), and it could precede the development of the endothelial dysfunction and insulin resistance (27). This points to the possibility that CRP may be involved in the development of diabetes.

We also have to consider the genetic factors of CRP. Recently, among non-smoking healthy adult women, FH is thought to be associated with increased plasma CRP levels (28); although in this study, there was no relationship between

FH and CRP in either sex. It is hypothesized that there may be a genetic relationship between CRP and diabetes, even though it is unclear whether a common genetic factor really exists. To understand the relationship between CRP and type 2 diabetes, further study is needed.

Several limitations of this study remained. First, anti-inflammatory medication might not have been considered completely in this study, although subjects were free of inflammatory diseases. Second, the definitions of inflammatory diseases tend to be transitional. Accordingly, whether the subjects were excluded by exactly the same criteria is uncertain.

CRP levels in nondiabetic Japanese Americans were slightly lower compared with Caucasians but higher than those in native Japanese populations. This suggests that westernization of lifestyle may cause a high CRP level. This report demonstrated that among Japanese Americans, CRP is considered a risk factor for diabetes independent of obesity or insulin resistance. It is suggested that the mechanism of diabetes development may be related to inflammation.

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