

Relationship Between C-Reactive Protein and Glucose Levels in Community-Dwelling Subjects Without Diabetes

The Hisayama Study

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C-reactive protein (CRP), a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease (1,2). It has also been reported that serum CRP levels are elevated in patients with impaired glucose tolerance (IGT) (3) or diabetes (4). A few prospective studies have shown that increased CRP levels are an independent risk factor for future diabetes (5,6). Although these findings indicate that CRP levels in peripheral blood are closely associated with glucose levels, it remains unclear whether a relationship exists between CRP levels and plasma glucose levels in the pre-diabetic range. The purpose of the present study was to investigate the relationship between CRP concentrations and pre-diabetic plasma glucose levels in a general Japanese population.

RESEARCH DESIGN AND METHODS

A population-based prospective study of cardiovascular disease has been underway since 1961 in the town of Hisayama, Kyushu Island, Japan. In 1988, as a part of the study, a cross-sectional diabetes survey of Hisayama residents was conducted (7). Of all 3,227 residents aged 40–79 years in the town

registry, 2,587 (80.2%) consented to take part in a comprehensive assessment, including a fasting 75-g oral glucose tolerance test. After excluding 82 nonfasting participants, 15 of whom failed to complete the oral glucose tolerance test, 302 with diabetes based on the American Diabetes Association (ADA) criteria (8), and 61 without serum samples for the CRP measurement, the final study group included 2,127 subjects (882 men and 1,245 women).

Overnight fasting and 2-h postload plasma glucose levels were determined by the glucose-oxidase method, and serum insulin was determined by radioimmunoassay. Total cholesterol, HDL cholesterol, and triglycerides were all determined enzymatically. Serum specimens collected at the time of the CRP measurement were stored at -20°C until 2002. High-sensitivity CRP was analyzed using a modification of the Behring Latex-Enhanced CRP assay on the Behring Nephelometer Analyzer System with a 2% interassay coefficient of variation. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg and/or current treatment with antihypertensive

agents. A questionnaire investigated smoking habits and alcohol intake, and both were classified as either currently or not currently habitual.

Because the distributions of CRP, fasting insulin, and triglycerides are skewed, these variables were natural log transformed for statistical analysis. The multivariate-adjusted CRP values were calculated by the covariance method and were compared by the Fisher's least significant difference method.

This study was conducted with the approval of the Ethics Committee of Kyushu University, and written informed consent was obtained from each participant.

RESULTS— The mean age was 57 years for both men and women. When the subjects were divided into three groups according to fasting plasma glucose levels, low (<5.6 mmol/l), modest (5.6–6.0 mmol/l), and high (6.1–6.9 mmol/l), the age- and sex-adjusted mean CRP levels significantly increased as the fasting glucose levels rose (0.41 mg/l in low, 0.49 mg/l in modest, and 0.62 mg/l in high fasting glucose level), and the differences between low and modest or high glucose levels were significant ($P < 0.01$). A similar pattern was observed for three 2-h postload glucose levels: low (<5.6 mmol/l), modest (5.6–7.7 mmol/l), and high (7.8–11.0 mmol/l). The age- and sex-adjusted CRP levels were 0.35 mg/l for low, 0.48 mg/l for modest, and 0.59 mg/l for the high postload glucose levels; the values were significantly higher for modest or high levels than for low levels ($P < 0.001$).

To clarify the existence of an independent relationship between each glucose level and CRP, we classified subjects into nine categories according to glucose levels measured at fasting and at 2-h postload and estimated mean CRP level in each category after adjustments for age, sex, fasting insulin, BMI, total cholesterol,

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Abbreviations: ADA, American Diabetes Association; CRP, C-reactive protein; IGT, impaired glucose tolerance.

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

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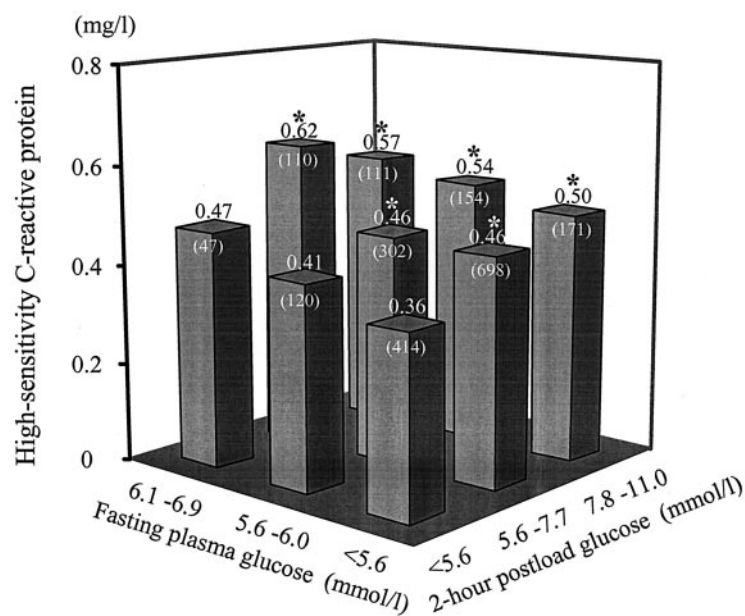


Figure 1—High-sensitivity C-reactive protein (CRP) levels according to fasting plasma glucose and 2-h postload glucose levels. Multivariate adjustments were made for age, sex, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, hypertension, smoking habits, and alcohol intake. Parentheses indicate the number of subjects. * $P < 0.05$ vs. category with fasting plasma glucose < 5.6 mmol/l and 2-h postload glucose < 5.6 mmol/l.

HDL cholesterol, triglycerides, hypertension, smoking habits, and alcohol intake (Fig. 1). When compared with the category of fasting and postload glucose levels of < 5.6 mmol/l, the adjusted CRP levels were significantly higher in the categories of IGT (high postload glucose levels, 7.8–11.0 mmol/l) and the modest postload glucose range (5.6–7.7 mmol/l), irrespective of fasting glucose levels.

CONCLUSIONS—The ADA recently proposed new criteria for diabetes and a lesser degree of impaired glucose regulation, although the criteria to diagnose diabetes and IGT remained as previously defined (8). However, the lower cut-off point defining impaired fasting glucose was reduced from ≥ 6.1 to ≥ 5.6 mmol/l. In our study, CRP progressively increased as fasting or postload glucose levels increased. These relationships did not show threshold effects, and CRP levels apparently rose even with the fasting glucose levels corresponding to the newly extended range of the impaired fasting glucose category (5.6–6.0 mmol/l) or with the postload glucose levels under the IGT category (5.6–7.7 mmol/l). These findings support the concept of the new ADA criteria for impaired fasting glucose, in which the expanded range of impaired

fasting glucose predicts future diabetes and cardiovascular disease (8). However, when analyzing fasting plasma glucose and 2-h postload glucose levels together, it is apparent that the elevated CRP levels in the new range, as well as in the range of impaired fasting glucose previously defined (6.1–6.9 mmol/l), are mainly due to elevated CRP concentrations according to 2-h postload glucose levels. These findings suggest that the glucose-CRP relationship is stronger for 2-h postload glucose levels than for fasting glucose levels. This hypothesis is in accordance with the findings of previous studies (9,10) showing the predominance of the effects of 2-h postload glucose levels on cardiovascular events.

A limitation is that CRP was measured by a long-term conserved serum at -20°C . It was however confirmed in the Reykjavik Study (11) that CRP concentrations were stable in preserved serum at this temperature for an average of 12 years.

To our knowledge, this is the first report to indicate a direct, positive relationship between CRP and pre-diabetic glucose levels across the normal range. Due to the cross-sectional design of the present study, however, we cannot infer from these results whether this relation-

ship is one of cause or effect. Prospective studies are needed to resolve this question.

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