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Original Research

Association Between Elevated C-Reactive Protein Levels and Prediabetes in Adults, Particularly Impaired Glucose Tolerance

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Key Messages

- Several studies have revealed an association between C-reactive protein levels and prediabetes.
- We conducted an in-depth study of C-reactive protein levels in Japanese subjects with differing glycemic statuses.
- Prediabetes was defined as impaired glucose tolerance, impaired fasting glucose or elevated hemoglobin A1C.
- Elevated C-reactive protein was associated with each prediabetes status.
- C-reactive protein was found to be consistently associated with impaired glucose tolerance levels rather than with impaired fasting glucose or elevated hemoglobin A1C levels.

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ABSTRACT

Objectives: Prediabetes is a precursor of diabetes and increases the risk for cardiovascular disease. A high C-reactive protein (CRP) level is a risk factor for diabetes, and individuals with prediabetes have higher CRP levels than those with normal glucose tolerance. In addition, systemic inflammation may play a role in the early-phase deterioration of glucose metabolism. We examined the association between serum CRP levels and prediabetes.
Methods: Overall, 4,101 subjects without diabetes underwent oral glucose tolerance tests. Levels of serum CRP were divided into quartiles; the lowest quartile was used as the reference when calculating odds ratios (ORs) and confidence intervals. Isolated fasting glucose, isolated glucose tolerance and elevated glycated hemoglobin levels (i.e. between 42 and 47 mmol/mol [6.0% to 6.4%]) were indicative of prediabetes.
Results: In the multiple logistic regression analysis, the ORs (95% confidence intervals) for impaired glucose tolerance, impaired fasting glucose and elevated glycated hemoglobin levels corresponding to the highest quartile of CRP levels were 1.67 (1.31 to 2.14); 1.62 (1.15 to 2.28); and 1.47 (1.14 to 1.90), respectively. In the stratified analysis, the ORs for impaired glucose tolerance were consistently higher in the uppermost quartile than in the reference quartile in both the presence and absence of hypertension or dyslipidemia. In contrast, the ORs for impaired fasting glucose in the uppermost quartile were higher only in the presence of hypertension and dyslipidemia, and the OR for elevated glycated hemoglobin levels in the uppermost quartile was higher only in the presence of hypertension.
Conclusions: Elevated serum CRP levels are associated with prediabetes, particularly impaired glucose tolerance.

Mots clés :
protéine C réactive
anomalie de la tolérance au glucose
inflammation
prédiabète

RÉSUMÉ

Objectifs : Le prédiabète est un état précurseur du diabète et augmente le risque de maladie cardiovasculaire. Un niveau élevé de protéine C réactive (CRP) est un facteur de risque pour le développement du diabète, et les individus avec un prédiabète ont des niveaux plus élevés de CRP que ceux ayant une tolérance normale au glucose. En outre, l'inflammation systémique peut jouer un rôle durant la phase précoce de la dégradation du métabolisme du glucose. Nous avons examiné l'association entre les taux sériques de CRP et le prédiabète.

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Méthodes : Dans l'ensemble, 4 101 sujets sans diabète ont subi des tests oraux de tolérance au glucose. Les niveaux de CRP sérique ont été divisés en quartiles; le quartile inférieur a servi de référence pour le calcul des rapports de cotes (ORs) et des intervalles de confiance. Une glycémie à jeun isolée, une tolérance au glucose isolée et des taux élevés d'hémoglobine glyquée (c'est-à-dire entre 42 et 47 mmol/mol [6,0% à 6,4%]) étaient indicatifs d'un état de prédiabète.
Résultats : Dans l'analyse de régression logistique multiple, les ORs (intervalles de confiance à 95%) pour une anomalie de la tolérance au glucose, une anomalie de la glycémie à jeun et des taux élevés d'hémoglobine glyquée correspondant au quartile supérieur des niveaux de CRP étaient respectivement de 1,67 (1,31 à 2,14); 1,62 (1,15 à 2,28); et 1,47 (1,14 à 1,90). Dans l'analyse stratifiée, les ORs pour l'intolérance au glucose étaient systématiquement plus élevés dans le quartile supérieur que dans le quartile de référence, tant en présence qu'en absence d'hypertension ou de dyslipidémie. En revanche, les ORs pour une anomalie de la glycémie à jeun dans le quartile supérieur n'étaient plus élevés qu'en présence d'hypertension et de dyslipidémie, et l'OR pour les taux élevés d'hémoglobine glyquée dans le quartile supérieur n'était plus élevé qu'en présence d'hypertension. Conclusions: Des taux sériques élevés de CRP sont associés au prédiabète, en particulier avec une anomalie de la tolérance au glucose.

Introduction

Type 2 diabetes is an established risk factor for cardiovascular disease (1). Additional risk factors incude impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and glycated hemoglobin (A1C) levels between 42 and 47 mmol/mol (6.0% to 6.4%). All 3 factors are associated with prediabetes, the precursor of diabetes. IGT is defined as a 2-h postload plasma glucose (2-h PG) level ≥6.1 mmol/L (140 mg/dL) (2), and IFG is defined as a fasting glucose level of 6.1 to 6.9 mmol/L (110 to 125 mg/dL) (3–5). High 2-h PG levels were found to be associated with increased cardiovascular mortality, even in subjects with normal glucose tolerance (NGT) (6).

Low-grade chronic inflammation and immunity play key roles in the pathophysiology of glucose disorders (7,8), and C-reactive protein (CRP) is a general systemic inflammatory marker. Elevated CRP levels were found to be correlated with an increased risk for diabetes in several studies, including a recent systematic review and meta-analysis (9–12), and with increased 2-h PG and fasting glucose levels in cross-sectional studies (13–15). Whether CRP levels also correlate with prediabetes is unclear owing to the availability of only a few studies that include relatively small sample sizes. Therefore, this study aimed to evaluate the association between serum CRP levels and prediabetes in a large Japanese population.

Methods

Study subjects

We analyzed a database of 4,362 subjects who underwent intensive health check-ups between 2004 and 2010 at Ota Memorial Hospital, Ota City, Gunma, Japan. All subjects listed in the database were local residents or workers employed in the car-manufacturing industry, and almost all had undergone oral glucose tolerance tests. We excluded 196 subjects with histories of diabetes or diagnoses of diabetes based on laboratory test results, and 1 subject with incomplete data. Because CRP levels >10 mg/L may be attributable to systemic infections (16,17), 64 subjects with CRP levels >10 mg/L were also excluded. Ultimately, our study population comprised 4,101 subjects. This study was approved by the Institutional Review Board of Ota Memorial Hospital. Because there was no personal information in our database, the ethics committee waived the requirement for informed consent.

Evaluations and definitions

All subjects underwent anthropometric evaluation, including body mass index (BMI). The BMIs were calculated as the weight (kg) divided by the height (m) squared. Systolic and diastolic blood pressures were determined by using a sphygmomanometer (Nippon COLIN BP-103i II, Tokyo, Japan); 2 consecutive values were recorded with 5-min intervals of quiet rest in the sitting position between the 2 measurements, and the average was used in the analysis.

Venous blood was collected after overnight fasting. The serum levels of CRP, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and plasma glucose were measured by using an automated analyzer (AU2700; Olympus, Tokyo, Japan). A1C levels were measured by using the latex coagulation method. The A1C values in the database were recorded in the format used by the Japan Diabetes Society and were converted by using the formula recommended by the National Glycohemoglobin Standardization Program: A1C (%)=1.02×A1C (Japan Diabetes Society) (%) + 0.25 (18). A1C levels between 42 and 47 mmol/mol (6.0% to 6.4%) were indicative of prediabetes as stipulated in the National Institute for Health and Care Excellence guidelines and the International Expert Committee Report (19,20). A1C levels in this range are referred to as "elevated HbA1c levels."

Overweight/obesity was defined as a BMI ≥25.0 kg/m^2. Hypertension was identified by systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or the use of antihypertensive medications. Dyslipidemia was identified by low-density lipoprotein cholesterol levels ≥3.626 mmol/L (140 mg/dL), high-density lipoprotein cholesterol levels <1.036 mmol/L (40 mg/dL), triglyceride levels ≥1.695 mmol/L (150 mg/dL) or the use of lipid-lowering medications.

Oral glucose-tolerance test

All subjects underwent an oral glucose-tolerance test in the morning after an overnight fast. Blood samples were collected through an indwelling venous catheter before and 2 h after the ingestion of a standard dose (75 g) of glucose (Toleran G; Ajinomoto Pharmaceuticals, Tokyo, Japan), and the plasma glucose levels were measured. Subjects with diabetes, as determined via the oral glucose-tolerance test and A1C levels, were excluded from the study. Diabetes was defined according to the World Health Organization/International Diabetes Federation 2006 criteria (2) and the 2009 recommendations of the World Health Organization (21).

This study included subjects with NGT, isolated IFG (I-IFG), isolated IGT (I-IGT) and combined IFG/IGT (C-IFG/IGT). NGT was defined as a fasting plasma glucose (FPG) level <6.1 mmol/L (110 mg/dL) and a 2-h PG level <7.8 mmol/L (140 mg/dL). I-IFG was defined as an FPG level of 7.8 to 11.0 mmol/L (110 to 126 mg/dL), and a 2-h PG level <7.8 mmol/L (140 mg/dL). I-IGT was defined as an FPG level <6.1 mmol/L (110 mg/dL), and the 2-h PG level was defined as 7.8 to 11.0 mmol/L (140 to 200 mg/dL). For C-IFG/IGT, the FPG level

was 7.8 to 11.0 mmol/L (110 to 126 mg/dL) and a 2-h PG level ranging between 7.8 and 11.0 mmol/L (140 to 200 mg/dL).

Statistical analyses

All statistical analyses were performed by using SPSS 21.0 software (IBM SPSS Statistics, Tokyo, Japan). Continuous variables are expressed as mean ± standard deviation, and variables with a skewed distribution (CRP and triglycerides) as a median (interquartile range). Categorical data are expressed as a percentage of the total. Continuous variables were determined according to glycemic status or quartiles of serum CRP levels and were compared by using an analysis of variance and the Kruskal-Wallis test, respectively. Post hoc analyses of the multiple comparisons were performed by using the Bonferroni correction. Categorical variables measured in those categories were compared by using the chi-square test. Logistic regression analyses were used to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for IGT (including I-IGT and C-IFG/IGT), IFG (including I-IFG and C-IFG/IGT), and elevated A1C levels after simultaneously controlling for potential confounders. Multiadjusted Model 1 included sex, age and BMI, and multiadjusted Model 2 included hypertension, dyslipidemia and current smoking as explanatory variables. We also performed analyses stratified by cardiovascular risk factors (age, sex, overweight/obesity, hypertension, dyslipidemia or current smoking). CRP levels were divided into quartiles, and the ORs were estimated using the lowest quartile as the reference. A p value <0.05 was considered to indicate statistical significance.

Results

Of the 4,101 subjects (3,107 men and 994 women; age range, 27 to 85 years) in our study, 3,239 had NGT, 171 had I-IFG, 550 had I-IGT and 141 had C-IFG/IGT. The characteristics of the study subjects according to glycemic status are shown in Table 1. Overall, averaged values were within the normal range. Subjects with I-IFG, I-IGT or C-IFG/IGT were older and had higher median levels of serum CRP (0.70 mg/L, p=0.015; 0.70 mg/L, p<0.001; and 0.70 mg/L, p<0.001, respectively) than subjects with NGT (0.50 mg/L). There were no significant differences in the serum CRP levels among the I-IFG, I-IGT and C-IFG/IGT groups. In addition, these groups had higher BMIs, systolic and diastolic blood pressures, A1C levels and triglyceride levels than the NGT group.

Table 2 shows the baseline characteristics of the study's subjects according to their quartiles of CRP levels. Age, BMI, systolic and diastolic blood pressure, current smoking prevalence as well as levels of FPG, 2-h PG, A1C, low-density lipoprotein cholesterol and triglycerides tended to increase as the serum CRP levels increased, whereas the high-density lipoprotein cholesterol levels tended to decrease. The distribution of the plasma glucose categories is shown in Supplementary Figure 1.

Multiadjusted logistic regression analysis using Model 2 showed that the highest (Q4; OR 1.67; 95% CI 1.31 to 2.14) and second highest (Q3; OR 1.33; 95% CI 1.04 to 1.70) quartiles of serum CRP levels were independently associated with the presence of IGT when compared with the lowest (reference) quartile (Q1; p for trend <0.001; Table 3). The highest quartile was also associated with IFG (OR 1.62; 95% CI 1.15 to 2.28), and elevated A1C (OR 1.47; 95% CI 1.14 to 1.90) levels.

In the stratified analyses, overweight/obese (BMI ≥25 kg/m^2) subjects in the upper 3 quartiles of serum CRP levels had significantly higher ORs for IGT than those in the reference quartile (Table 4, Supplementary Table 1). In contrast, among lean subjects, the OR for IGT was significant in the uppermost quartile only. Hence, the overall OR for IGT was much higher in obese subjects than in lean subjects. The stratified analyses of only lean (BMI <25 kg/m^2) subjects is shown in Supplementary Table 2.

In the analyses stratified for hypertension or dyslipidemia, the results differed according to the prediabetes indicator (IFG or IGT). The highest quartile of serum CRP levels showed a consistently higher OR for IGT than the reference quartile in the presence and absence of hypertension or dyslipidemia (Table 4). In contrast, the OR for IFG was higher in the presence compared with in the absence of hypertension or dyslipidemia. In subjects with hypertension, IFG was associated with the highest and second-highest quartiles of serum CRP levels (Q4: OR 2.18; 95% CI 1.22 to 3.89; and Q3: OR 1.87; 95% CI 1.03 to 3.37). In subjects with dyslipidemia, IFG was associated with the highest quartile only (OR 1.75; 95% CI 1.11 to 2.77). There was also a weak association between the quartiles of serum CRP levels and IFG in subjects without hypertension or dyslipidemia. Elevated A1C levels increased the OR for IFG in subjects with hypertension. In subjects with hypertension, the highest quartile of serum

Table 1
Characteristics of the study's subjects

	Overall	NGT	I-IFG	I-IGT	C-IFG/IGT	p value
N	4,101	3,239	171	550	141	
Male (%)	3,107 (75.8)	*146 (85.4)	*448 (81.5)	*126 (89.4)	<0.001	
Age (years)	53±10	52±10	*55±8	*56±10	†55±9	<0.001
BMI (kg/m^2)	23.4±3.0	23.2±2.8	†23.9±3.2	*24.3±3.3	*25.2±2.9	<0.001
Systolic BP (mmHg)	128±16	119±15	*127±16	*125±15	*128±16	<0.001
Diastolic BP (mmHg)	73±11	72±11	*77±11	*76±10	*79±11	<0.001
Fasting PG (mmol/L)	5.33±0.50	5.22±0.42	*6.33±0.22	*5.43±0.38	*6.40±0.24	<0.001
2-h PG (mmol/L)	6.37±1.50	5.85±1.05	*6.27±1.00	*8.74±0.82	*9.08±0.96	<0.001
A1C (mmol/mol)	38±3	37±3	*40±3	*39±3	*42 3	<0.001
A1C (%)	5.6±0.3	5.6±0.3	5.8±0.3	5.7±0.3	6.0±0.3	
LDL cholesterol (mmol/L)	3.30±0.76	3.29±0.75	3.29±0.82	3.33±0.81	3.42±0.77	0.11
HDL cholesterol (mmol/L)	1.49±0.37	1.51±0.37	1.48±0.37	*1.40±0.35	*1.34±0.31	<0.001
Triglycerides (mmol/L)	1.16 (0.85, 1.67)	1.11 (0.82, 1.59)	†1.22 (0.93, 1.75)	*1.45 (1.02, 1.99)	*‡1.58 (1.10, 2.08)	<0.001
Current smoking, n (%)	1107 (27.0)	884 (27.3)	45 (26.3)	144 (26.2)	34 (24.1)	0.81
CRP (nmol/L)	4.7 (2.9, 9.5)	4.8 (2.9, 8.6)	†6.7 (2.9, 11.4)	*6.7 (3.8, 11.4)	*6.7 (3.8, 11.4)	<0.001
CRP (mg/L)	0.50 (0.30, 1.00)	0.50 (0.03, 0.90)	0.70 (0.30, 1.20)	0.70 (0.40, 1.30)	0.70 (0.40, 1.20)	

A1C, glycated hemoglobin; *BMI,* body mass index; *BP,* blood pressure; *C-IFG/IGT,* combined impaired fasting glucose and impaired glucose tolerance; *CRP,* C-reactive protein; *HDL,* high-density lipoprotein; *I-IFG,* isolated impaired fasting glucose; *I-IGT,* isolated impaired glucose tolerance; *LDL,* low-density lipoprotein; *NGT,* normal glucose tolerance; *PG,* plasma glucose.

Note: Data are expressed as mean ± standard deviation, median (interquartile range) or number (percentage of the total).

* p<0.001 compared with NGT subjects.

† p<0.05 compared with NGT subjects.

‡ p<0.01 compared with IFG subjects.

Table 2
Baseline characteristics of the study's subjects according to quartiles of serum C-reactive protein (CRP) levels

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p value
N	1,385	826	986	904	
Sex (male, %)	957 (69.1)	640 (77.5)	784 (79.5)	726 (80.3)	<0.001
Age (years)	52±10	53±9	53±10	54±10	0.004
BMI (kg/m^2)	22.2±2.5	23.3±2.7	24.1±2.8	24.6±3.3	<0.001
Systolic BP (mmHg)	117±15	120±15	122±16	124±16	<0.001
Diastolic BP (mmHg)	71±11	73±11	74±11	75±11	<0.001
Fasting PG (mmol/L)	5.28±0.48	5.32±0.51	5.35±0.51	5.41±0.52	0.002
2-h PG (mmol/L)	6.04±1.43	6.29±1.41	6.56±1.51	6.73±1.56	<0.001
A1C (mmol/mol)	37.4±3.1	37.7±3.3	38.0±3.3	38.5±3.2	<0.001
A1C (%)	5.6±0.3	5.6±0.3	5.6±0.3	5.7±0.3	
LDL cholesterol (mmol/L)	3.18±0.72	3.30±0.70	3.36±0.75	3.42±0.85	<0.001
HDL cholesterol (mmol/L)	1.61±0.38	1.51±0.36	1.42±0.33	1.36±0.33	<0.001
Triglycerides (mmol/L)	1.00 (0.75, 1.41)	1.14 (0.86, 1.63)	1.31 (0.93, 1.88)	1.33 (0.95, 1.86)	<0.001
Current smoking, n (%)	289 (20.9)	212 (25.7)	304 (30.8)	302 (33.4)	<0.001
CRP (nmol/L)	1.90 (0.95, 2.86)	3.81 (3.81, 4.76)	6.67 (5.71, 8.57)	16.19 (12.38, 25.71)	<0.001
CRP (mg/L)	0.20 (0.10, 0.30)	0.40 (0.40, 0.50)	0.70 (0.60, 0.90)	1.70 (1.30, 2.70)	

A1C, glycated hemoglobin; *BMI,* body mass index; *BP,* blood pressure; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *PG,* plasma glucose.
Note: Data are expressed as mean ± standard deviation, median (interquartile range) or number (percentage of the total).

Table 3
Association between quartiles of serum C-reactive protein (CRP) levels and prediabetes

	Quartiles of serum CRP levels				p for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
IGT					
Crude	1.00 (reference)	1.45 (1.13, 1.87)	1.92 (1.53, 2.42)	2.62 (2.09, 3.29)	<0.001
Model 1	1.00 (reference)	1.18 (0.91, 1.53)	1.39 (1.10, 1.77)	1.74 (1.37, 2.22)	<0.001
Model 2	1.00 (reference)	1.16 (0.89, 1.51)	1.33 (1.04, 1.70)	1.67 (1.31, 2.14)	<0.001
IFG					
Crude	1.00 (reference)	1.60 (1.12, 2.28)	1.86 (1.33, 2.59)	2.39 (1.73, 3.30)	<0.001
Model 1	1.00 (reference)	1.33 (0.92, 1.91)	1.40 (1.00, 1.97)	1.68 (1.19, 2.36)	0.035
Model 2	1.00 (reference)	1.31 (0.91, 1.89)	1.34 (0.95, 1.89)	1.62 (1.15, 2.28)	0.0086
Elevated A1C					
Crude	1.00 (reference)	1.50 (1.16, 1.94)	1.72 (1.35, 2.18)	2.15 (1.70, 2.72)	<0.001
Model 1	1.00 (reference)	1.32 (1.02, 1.73)	1.38 (1.07, 1.77)	1.60 (1.24, 2.06)	<0.001
Model 2	1.00 (reference)	1.28 (0.99, 1.68)	1.27 (0.98, 1.64)	1.47 (1.14, 1.90)	0.0057

A1C, glycated hemoglobin; *CI,* confidence interval; *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance; *OR,* odds ratio.
Note: Data are expressed as OR (95% CI). Model 1 is adjusted for sex, age and body mass index; Model 2 is adjusted for sex, age, body mass index, hypertension, dyslipidemia and current smoking.

CRP levels was associated with elevated A1C levels (OR, 1.91; 95% CI 1.21 to 3.03; Supplementary Table 1).

Discussion

The main finding of the present study was the significant association between elevated serum CRP levels and prediabetes in middle-aged Japanese adults. CRP levels correlated significantly with IFG, IGT and elevated A1C levels, all of which are indicators of prediabetes.

Insulin resistance is an essential prerequisite for diabetogenesis (22). It is thought to represent a chronic inflammatory state (23,24) owing to its induction by tumor necrosis factor-alpha, a proinflammatory cytokine (25,26). Moreover, the presence of inflammation-induced insulin resistance in subjects without diabetes has been documented (27). Our data that associate elevated levels of CRP, a systemic inflammatory marker, with prediabetes are consistent with these findings, and we suggest that low chronic inflammation coexists with glucose intolerance owing to the bolstering of insulin resistance. Which prediabetes indicator is most closely associated with inflammation is unclear. In 2 previous studies, IGT better correlated with insulin resistance (and hence inflammation) than did IFG (28,29). In a cross-sectional study, IGT and diabetes, but not IFG, were associated with elevated levels of plasma interleukin-6, which is a key proinflammatory cytokine (30).

In our stratified analyses, CRP levels better correlated with IGT in overweight/obese subjects than in lean subjects. Given the strong association between obesity and insulin resistance, this finding is reasonable. Conversely, CRP levels more strongly correlated with IFG in lean subjects than in overweight/obese subjects.

CRP levels strongly correlated with IGT in both the presence and the absence of hypertension or dyslipidemia. On the other hand, they strongly correlated with IFG only in the presence of hypertension or dyslipidemia. These findings are consistent with those of a previous report (31) and are indicative of a strengthening effect of hypertension and dyslipidemia on the association between chronic inflammation and prediabetes. A robust association between the CRP levels and elevated A1C levels was also observed in subjects with hypertension.

The present study demonstrates the presence of chronic inflammation in subjects with prediabetes, particularly those with IGT. Recent studies have shown that even 2-h PG levels in the high-normal range can increase the risk for cardiovascular disease. Within normoglycemic range, subjects whose 2-h PG did not return to their FPG levels during an oral glucose tolerance test had increased risk of cardiovascular disease, resulting in a high baseline homeostasis model assessment of the insulin resistance index (32). We reported an association between high-normal 2-h PG levels and increased carotid artery intima-media thickness in subjects with NGT (33). These findings indicate that low-grade inflammation precedes the development of prediabetes.

Table 4
Association between quartiles of serum CRP levels and IFG/IGT stratified by cardiovascular risk factors

	Quartiles of serum CRP levels				p for trend	p for interaction
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
IGT						
Sex						
Men (n=3,107)	1.00 (reference)	1.17 (0.87, 1.57)	1.37 (1.04, 1.81)	1.76 (1.34, 2.32)	<0.001	0.83
Women (n=994)	1.00 (reference)	1.18 (0.67, 2.09)	1.24 (0.72, 2.16)	1.41 (0.80, 2.47)	0.23	
Age						
≥55 years (n=1,995)	1.00 (reference)	1.20 (0.85, 1.68)	1.28 (0.93, 1.76)	1.81 (1.32, 2.49)	<0.001	0.27
<55 years (n=2,106)	1.00 (reference)	1.15 (0.77, 1.74)	1.48 (1.02, 2.16)	1.65 (1.13, 2.41)	0.0049	
BMI						
≥25 kg/m^2 (n=1,110)	1.00 (reference)	1.33 (0.76, 2.32)	1.91 (1.16, 3.13)	2.73 (1.69, 4.41)	<0.001	0.40
<25 kg/m^2 (n=2,991)	1.00 (reference)	1.28 (0.95, 1.72)	1.38 (1.03, 1.83)	1.59 (1.18, 2.14)	0.0020	
Hypertension						
Yes (n=1,023)	1.00 (reference)	1.19 (0.76, 1.85)	2.05 (1.32, 3.19)	1.59 (1.02, 2.49)	0.0089	0.12
No (n=3,078)	1.00 (reference)	1.12 (0.82, 1.53)	1.08 (0.79, 1.49)	1.75 (1.31, 2.33)	<0.001	
Dyslipidemia						
Yes (n=2,183)	1.00 (reference)	1.19 (0.86, 1.64)	1.65 (1.20, 2.28)	1.64 (1.18, 2.28)	0.0070	0.98
No (n=1,918)	1.00 (reference)	1.31 (0.86, 2.00)	0.95 (0.61, 1.50)	1.65 (1.09, 2.52)	0.52	
Current smoking						
Yes (n=1,107)	1.00 (reference)	1.15 (0.68, 1.96)	0.94 (0.57, 1.56)	1.50 (0.93, 2.43)	0.13	0.052
No (n=2,994)	1.00 (reference)	1.14 (0.84, 1.54)	1.49 (1.12, 1.96)	1.69 (1.27, 2.25)	<0.001	
IFG						
Sex						
Men	1.00 (reference)	1.07 (0.72, 1.58)	1.23 (0.85, 1.77)	1.36 (0.94, 1.97)	0.077	0.032
Women	1.00 (reference)	4.32 (1.58, 11.86)	2.11 (0.68, 6.53)	4.91 (1.78, 13.58)	0.0088	
Age						
≥55 years	1.00 (reference)	1.31 (0.82, 2.10)	1.16 (0.73, 1.83)	1.73 (1.11, 2.69)	0.032	0.14
<55 years	1.00 (reference)	1.38 (0.78, 2.48)	1.68 (0.98, 2.86)	1.68 (0.97, 2.89)	0.055	
BMI						
≥25 kg/m^2	1.00 (reference)	1.50 (0.74, 1.75)	1.32 (0.69, 2.53)	1.52 (0.81, 2.86)	0.82	0.26
<25 kg/m^2	1.00 (reference)	1.33 (0.87, 2.05)	1.50 (0.99, 2.26)	1.96 (1.30, 2.96)	0.017	
Hypertension						
Yes	1.00 (reference)	1.15 (0.62, 2.11)	1.87 (1.03, 3.37)	2.18 (1.22, 3.89)	0.0022	0.32
No	1.00 (reference)	1.42 (0.92, 2.19)	1.13 (0.72, 1.78)	1.34 (0.87, 2.06)	0.33	
Dyslipidemia						
Yes	1.00 (reference)	1.43 (0.92, 2.21)	1.52 (0.97, 2.41)	1.75 (1.11, 2.77)	0.021	0.93
No	1.00 (reference)	0.85 (0.46, 1.59)	0.94 (0.51, 1.75)	1.34 (0.75, 2.41)	0.23	
Current smoking						
Yes	1.00 (reference)	1.54 (0.69, 3.47)	1.82 (0.87, 3.82)	1.30 (0.60, 2.80)	0.59	0.11
No	1.00 (reference)	1.27 (0.85, 1.92)	1.19 (0.80, 1.77)	1.80 (1.23, 2.66)	0.0060	

BMI, body mass index; *CI,* confidence interval; *CRP,* C-reactive protein; *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance; *OR,* odds ratio.
Note: Data are expressed as OR (95% CI); adjusted for sex, age, BMI, hypertension, dyslipidemia and current smoking (without stratified parameters).

This study had a few limitations. First, it included only a small number of women, and the database used was hospital derived. Therefore, the results cannot be extrapolated to the general population. Second, serum insulin levels were not examined. Third, there was no information about comorbidities, socioeconomic status, alcohol consumption or family history of diabetes and cardiovascular disease. Fourth, this study was a cross-sectional design; thus, causation could not be inferred. Despite these limitations, the study also provided noteworthy information. By consolidating the data obtained from oral glucose-tolerance tests performed during health check-ups of relatively healthy subjects, we were able to demonstrate the coexistence of inflammation and prediabetes. We note that previous cross-sectional studies have reported an association between CRP levels and glycemic status in the Asian population (34–36). However, the sample population in these studies was relatively small and included only individuals with data regarding NGT or IGT; moreover, detailed patient information was lacking. Our in-depth study assessed CRP levels in a large cohort of Japanese subjects with differing glycemic statuses.

Conclusions

Elevated CRP levels are significantly associated with prediabetes, particularly with IGT, in middle-aged Japanese adults. This finding may provide evidence for the presence of inflammation with prediabetes, particularly IGT, in Japanese subjects. Further studies should assess the role of inflammation in prediabetes so as to prevent complications of diabetes such as cardiovascular diseases.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of *Canadian Journal of Diabetes* at https://www.canadianjournalofdiabetes.com.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

K.K. and T.O. contributed to the study design and writing of the paper. N.K., T.N., Y.K. and T.K. contributed to the data collection. K.K. analyzed the collected data. T.O., Y.S. and T.K. revised the manuscript.

All authors have read the manuscript and approved its submission.

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Supplementary Material

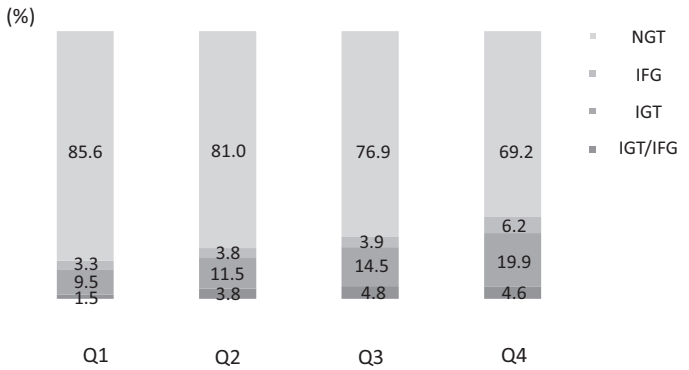

Figure S1. Distribution of plasma glucose categories by C-reactive protein quartiles. *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance; *NGT,* normal glucose tolerance.

Table S1
Association between quartiles of serum CRP levels and elevated A1C stratified by cardiovascular risk factors

	Quartiles of serum CRP levels				p for trend	p for interaction
Elevated A1C	Q1	Q2	Q3	Q4		
Sex						
Men (n=3,107)	1.00 (reference)	1.38 (0.99, 1.92)	1.46 (1.07, 1.99)	1.75 (1.28, 2.39)	<0.001	0.83
Women (n=994)	1.00 (reference)	1.24 (0.78, 1.98)	0.98 (0.61, 1.57)	0.99 (0.60, 1.62)	0.87	
Age						
≥55 years (n=1,995)	1.00 (reference)	1.24 (0.89, 1.71)	1.20 (0.88, 1.63)	1.38 (1.00, 1.89)	0.067	0.27
<55 years (n=2,106)	1.00 (reference)	1.51 (0.95, 2.40)	1.56 (1.00, 2.44)	1.99 (1.28, 3.08)	0.0030	
BMI						
≥25 kg/m^2 (n=1,110)	1.00 (reference)	1.45 (0.80, 2.61)	1.58 (0.93, 2.69)	2.18 (1.30, 3.64)	0.0016	0.40
<25 kg/m^2 (n=2,991)	1.00 (reference)	1.37 (1.02, 1.85)	1.33 (0.99, 1.80)	1.38 (1.01, 1.89)	0.033	
Hypertension						
Yes (n=1,023)	1.00 (reference)	1.44 (0.86, 2.40)	1.17 (0.72, 1.91)	1.91 (1.21, 3.03)	0.011	0.12
No (n=3,078)	1.00 (reference)	1.24 (0.91, 1.70)	1.34 (0.99, 1.80)	1.27 (0.92, 1.74)	0.10	
Dyslipidemia						
Yes (n=2,183)	1.00 (reference)	1.47 (1.05, 2.06)	1.29 (0.94, 1.78)	1.49 (1.08, 2.06)	0.040	0.98
No (n=1,918)	1.00 (reference)	1.03 (0.66, 1.60)	1.26 (0.82, 1.94)	1.47 (0.96, 2.26)	0.060	
Current smoking						
Yes (n=1,107)	1.00 (reference)	1.36 (0.74, 2.51)	1.48 (0.84, 2.60)	1.51 (0.86, 2.65)	0.17	0.052
No (n=2,994)	1.00 (reference)	1.28 (0.95, 1.73)	1.22 (0.91, 1.63)	1.48 (1.11, 1.99)	0.015	

A1C, glycated hemoglobin; *BMI,* body mass index; *CI,* confidence interval; *CRP,* C-reactive protein; *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance; *OR,* odds ratio; *Q,* quartile.
Note: Data are expressed as OR (95% CI). Adjusted for sex, age, BMI, hypertension, dyslipidemia and current smoking (without stratified parameter).

Table S2
Association between quartiles of serum CRP levels and prediabetes with lean subjects stratified by cardiovascular risk factors

	Quartiles of serum CRP levels				p for trend
	Q1	Q2	Q3	Q4	
IGT					
Sex					
Men (n=2186)	1.00 (reference)	1.15 (0.79, 1.68)	1.17 (0.81, 1.70)	1.57 (1.09, 2.25)	0.014
Women (n=805)	1.00 (reference)	1.58 (0.84, 2.95)	1.17 (0.58, 2.36)	1.47 (0.73, 2.96)	0.46
Age					
≥55 years (n=1550)	1.00 (reference)	1.29 (0.86, 1.93)	1.31 (0.87, 1.95)	1.61 (1.08, 2.40)	0.025
<55 years (n=1441)	1.00 (reference)	1.21 (0.71, 2.05)	1.00 (0.57, 1.76)	1.66 (0.98, 2.80)	0.10
Hypertension					
Yes (n=621)	1.00 (reference)	1.41 (0.75, 2.66)	1.49 (0.81, 2.74)	1.64 (0.99, 2.97)	0.12
No (n=2370)	1.00 (reference)	1.17 (0.81, 1.70)	1.06 (0.72, 1.57)	1.51 (1.04, 2.21)	0.055
Dyslipidemia					
Yes (n=1436)	1.00 (reference)	1.05 (0.66, 1.65)	1.23 (0.79, 1.90)	1.54 (1.00, 2.37)	0.026
No (n=1555)	1.00 (reference)	1.42 (0.90, 2.23)	1.06 (0.64, 1.75)	1.47 (0.91, 2.37)	0.26
Current smoking					
Yes (n=781)	1.00 (reference)	1.28 (0.62, 2.67)	1.32 (0.65, 2.68)	1.57 (0.79, 3.11)	0.20
No (n=2210)	1.00 (reference)	1.21 (0.84, 1.73)	1.11 (0.77, 1.61)	1.54 (1.07, 2.21)	0.037
IFG					
Sex					
Men	1.00 (reference)	0.96 (0.59, 1.65)	1.36 (0.84, 2.20)	1.35 (0.83, 2.20)	0.12
Women	1.00 (reference)	1.53 (0.48, 4.86)	0.86 (0.22, 3.41)	3.25 (1.07, 9.84)	0.51
Age					
≥55 years	1.00 (reference)	1.23 (0.70, 2.16)	1.21 (0.68, 2.13)	1.80 (1.05, 3.09)	0.035
<55 years	1.00 (reference)	0.78 (0.33, 1.84)	1.65 (0.78, 3.53)	1.22 (0.55, 2.72)	0.30
Hypertension					
Yes	1.00 (reference)	1.14 (0.49, 2.64)	1.34 (0.60, 3.00)	1.89 (0.89, 4.04)	0.067
No	1.00 (reference)	1.02 (0.58, 1.79)	1.32 (0.76, 2.29)	1.41 (0.81, 2.47)	0.15
Dyslipidemia					
Yes	1.00 (reference)	1.27 (0.65, 2.48)	1.95 (1.05, 3.62)	1.82 (0.97, 3.40)	0.030
No	1.00 (reference)	0.90 (0.46, 1.76)	0.73 (0.35, 1.52)	1.41 (0.74, 2.69)	0.36
Current smoking					
Yes	1.00 (reference)	1.08 (0.34, 3.44)	2.24 (0.78, 6.29)	1.15 (0.39, 3.40)	0.65
No	1.00 (reference)	1.08 (0.65, 1.81)	1.08 (0.64, 1.83)	1.80 (1.10, 2.94)	0.019
Elevated A1C					
Sex					
Men	1.00 (reference)	1.37 (0.87, 2.15)	1.94 (1.27, 2.97)	1.86 (1.21, 2.86)	0.0017
Women	1.00 (reference)	1.11 (0.67, 1.84)	0.87 (0.50, 1.53)	0.77 (0.43, 1.39)	0.29
Age					
≥55 years	1.00 (reference)	1.35 (0.91, 2.00)	1.52 (1.03, 2.24)	1.55 (1.04, 2.30)	0.031
<55 years	1.00 (reference)	1.07 (0.58, 1.98)	1.43 (0.78, 2.61)	1.29 (0.69, 2.41)	0.29
Hypertension					
Yes	1.00 (reference)	1.68 (0.87, 3.23)	1.09 (0.56, 2.12)	1.56 (0.84, 2.92)	0.38
No	1.00 (reference)	1.13 (0.77, 1.67)	1.63 (1.12, 2.38)	1.32 (0.88, 1.96)	0.061
Dyslipidemia					
Yes	1.00 (reference)	1.36 (0.86, 2.14)	1.84 (1.20, 2.84)	1.42 (0.91, 2.23)	0.082
No	1.00 (reference)	1.11 (0.68, 1.81)	0.98 (0.58, 1.67)	1.40 (0.85, 2.32)	0.27
Current smoking					
Yes	1.00 (reference)	1.26 (0.51, 3.11)	2.50 (1.09, 5.73)	1.76 (0.76, 4.05)	0.11
No	1.00 (reference)	1.27 (0.89, 1.82)	1.27 (0.88, 1.83)	1.35 (0.93, 1.96)	0.14

A1C, glycated hemoglobin; *CI*, confidence interval; *CRP*, C-reactive protein; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *OR*, odds ratio; *Q*, quartile.
Note: Data are expressed as OR (95% CI); adjusted for sex, age, body mass index, hypertension, dyslipidemia and current smoking (without stratified parameter).