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Association between fasting plasma glucose and high-sensitivity C-reactive protein: gender differences in a Japanese community-dwelling population

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Abstract

Background: High sensitivity C-reactive protein (hsCRP) is an acute phase reactant and a sensitive marker of inflammation. Hyperglycemia can potentially promote the production of CRP. The aim of this study was to determine whether increased fasting plasma glucose (FPG) levels are associated with elevated hsCRP concentrations by gender.

Methods: We recruited 822 men (mean age, 61 ± 14 years) and 1,097 women (63 ± 12 years) during their annual health examination from a single community. We cross-sectionally examined whether FPG levels are associated with hsCRP concentrations, and whether this association is independent of gender, body mass index (BMI) and other components of the metabolic syndrome.

Results: In women only, hsCRP increased significantly and progressively with increasing FPG ($r = 0.169$, $P < 0.001$). The stepwise multiple linear regression analysis using hsCRP as an objective variable, adjusted for confounding factors as explanatory variables, showed that FPG as well as age, BMI, systolic blood pressure, high-density lipoprotein cholesterol (HDL-C), uric acid, and high molecular weight adiponectin were significantly associated with hsCRP in women, but not in men. There was significant gender interaction, and an increase in hsCRP levels that was greater in women with BMI ≥ 25 kg/m^2 and higher FPG than in men.

Conclusions: These results suggested that hsCRP levels increase continuously across the FPG spectrum starting from the lowest FPG in both men and women. However, increase in hsCRP levels was greater in women than men.

Keywords: C-reactive protein, fasting plasma glucose, type 2 diabetes, gender interaction, risk factor

Introduction

C-reactive protein (CRP) is an acute phase reactant and a sensitive marker of inflammation. Several studies support the concept that high-sensitivity C-reactive protein (hsCRP), even when within the clinical normal range, is an important precursor of the metabolic syndrome (MetS) and type 2 diabetes [1-3], and it may be an independent predictor that reflects early stage cardiovascular disease (CVD) [4-6].

A recent review of 20 studies revealed that there was also a significant exponential association between glucose and CVD in nondiabetic participants that extended below the usual "diabetic threshold" [7], and fasting plasma glucose (FPG) is an important predictor of CVD after adjusting for potential confounders. Experimental studies have shown that hyperglycemia stimulates the release of the inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) from various cells such as monocytes [8]. Recent data have demonstrated that hsCRP is stimulated and produced in the liver by proinflammatory cytokines (e.g., TNF-α and IL-6) produced by visceral adiposity [9]. Thus, elevated FPG is associated with elevated concentrations of hsCRP [10-12].

On the other hand, Nakanishi et al. reported that hsCRP levels are much higher in Westerners than in Japanese [13], and in women compared with men [3,14]. In addition, gender differences have been reported to be consistent across all ethnic subgroups even after multivariable adjustment [14]. However, the question of whether modification by gender has an effect on the association between FPG and inflammation in Japanese has not been investigated in detail.

The aim of this study was to determine whether elevated FPG levels are associated with elevated hsCRP concentrations, and whether this association is independent of gender, body mass index (BMI) and other confounders of CVD. We examined cross-sectional data from Japanese community-dwelling participants.

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Table 1 Clinical characteristics of male participants according to fasting plasma glucose category

Men, N = 822	Normal fasting plasma glucose			IFG	Type-2 diabetes or >125 mg/dL	P-value*
Characteristics	FBS <90 N = 200	90-99 N = 286	100-109 N = 143	110-125 N = 63	N = 130	
Age (years)	57 ± 15	60 ± 14	63 ± 13	60 ± 12	66 ± 9	<0.001
Body mass index (kg/m^2)	22.6 ± 2.9	23.6 ± 2.8	24.5 ± 3.1	24.7 ± 3.2	23.8 ± 2.7	<0.001
Smoking status, %	29.0/19.5/51.5	46.9/22.7/30.4	43.4/29.4/27.3	44.4/28.6/27.0	46.2/30.8/23.1	<0.001
Alcohol consumption, %	15.0/33.0/52.0	12.9/31.8/55.2	17.5/20.3/62.2	3.2/22.2/74.6	20.0/26.2/53.8	0.005
History of CVD, %	7.0	9.1	10.5	9.5	15.4	0.160
Systolic blood pressure (mmHg)	130 ± 17	140 ± 20	147 ± 18	147 ± 19	147 ± 20	<0.001
Diastolic blood pressure (mmHg)	80 ± 10	84 ± 11	87 ± 11	90 ± 12	87 ± 10	<0.001
Antihypertensive medication, %	13.5	22.4	32.9	33.3	33.8	<0.001
Triglycerides (mg/dL)	91 (66-133)	94 (73-126)	104 (75-142)	105 (77-165)	96 (71-162)	0.014
HDL cholesterol (mg/dL)	59 ± 14	59 ± 14	60 ± 16	59 ± 16	58 ± 16	0.880
LDL cholesterol (mg/dL)	105 ± 31	111 ± 29	118 ± 34	107 ± 33	111 ± 33	0.003
Antilipidemic medication, %	2.5	3.5	4.9	1.6	6.9	0.229
Serum uric acid (mg/dL)	5.9 ± 1.2	6.0 ± 1.4	6.1 ± 1.4	6.2 ± 1.4	5.5 ± 1.4	<0.001
Fasting plasma glucose (mg/dL)	86 (83-88)	94 (92-96)	103 (101-105)	115 (112-118)	122 (100-150)	<0.001
Immuno-reactive insulin (μU/mL)	3.65 (2.00-5.48)	4.60 (3.20-6.90)	6.20 (3.50-8.30)	6.60 (4.70-8.70)	4.80 (3.30-8.20)	<0.001
Hypoglycemic medication, %	0	0	0	0	25.4	<0.001
HMW adiponectin (μg/mL)	3.65 (2.37-6.09)	3.41 (1.97-5.52)	3.66 (1.91-5.10)	2.67 (1.70-4.99)	3.03 (1.86-4.88)	0.030
hsCRP (mg/dL)	0.046 (0.026-0.096)	0.046 (0.025-0.104)	0.057 (0.028-0.112)	0.069 (0.042-0.150)	0.060 (0.035-0.117)	0.033

CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HMW, High molecular weight; hsCRP, high sensitivity C-reactive protein. Data presented are mean ± standard deviation. Data for triglycerides, fasting plasma glucose, HMW adiponectin, immuno-reactive insulin, and hsCRP were skewed, and are presented as median (interquartile range) and were log-transformed for analysis. *P-value: ANOVA or X^2 -test.

Table 2 Clinical characteristics of female participants according to fasting plasma glucose category

Women, N = 1,097 mg/dL	Normal fasting plasma glucose			IFG	Type-2 diabetes or >125 mg/dL	P-value*
Characteristics	FBS <90 N = 409	90-99 N = 391	100-109 N = 152	110-125 N = 52	N = 93	
Age (years)	58 ± 13	64 ± 10	67 ± 9	68 ± 9	66 ± 10	<0.001
Body mass index (kg/m^2)	22.5 ± 3.1	23.4 ± 3.2	24.4 ± 3.4	24.9 ± 3.8	24.6 ± 3.9	<0.001
Smoking status, %	97.1/0.7/2.2	98.5/0.5/1.0	95.4/2.0/2.6	98.1/1.9/0	98.9/0/1.1	0.409
Alcohol consumption, %	58.4/35.7/5.9	66.8/26.6/6.6	69.1/27.0/3.9	69.6/28.8/1.9	73.1/24.7/2.2	0.035
History of CVD, %	5.4	5.6	12.5	5.8	9.7	0.025
Systolic blood pressure (mmHg)	131 ± 22	141 ± 22	145 ± 24	151 ± 22	144 ± 23	<0.001
Diastolic blood pressure (mmHg)	77 ± 12	82 ± 11	83 ± 12	86 ± 11	81 ± 11	<0.001
Antihypertensive medication, %	15.6	23.5	38.2	50.0	44.1	<0.001
Triglycerides (mg/dL)	84 (61-114)	92 (69-128)	90 (70-135)	106 (78-144)	94 (70-155)	<0.001
HDL cholesterol (mg/dL)	66 ± 15	65 ± 15	65 ± 16	65 ± 15	61 ± 16	0.127
LDL cholesterol (mg/dL)	120 ± 29	127 ± 29	134 ± 30	131 ± 28	132 ± 31	<0.001
Antilipidemic medication, %	3.7	6.1	9.2	17.3	11.8	<0.001
Serum uric acid (mg/dL)	4.3 ± 1.0	4.5 ± 1.0	4.6 ± 1.1	4.8 ± 0.9	4.6 ± 1.1	<0.001
Fasting plasma glucose (mg/dL)	86 (82-88)	94 (92-97)	103 (101-105)	116 (113-120)	126 (103-150)	<0.001
Immuno-reactive insulin (μU/mL)	4.80 (3.40-6.80)	6.20 (4.50-8.60)	7.40 (5.25-11.5)	9.50 (6.75-12.9)	7.80 (5.20-11.2)	<0.001
Hypoglycemic medication, %	0	0	0	0	37.6	<0.001
HMW adiponectin (μg/mL)	7.15 (4.72-10.3)	6.82 (4.65-10.1)	5.94 (4.12-8.83)	4.82 (3.58-7.73)	5.22 (3.20-8.16)	<0.001
hsCRP (mg/dL)	0.035 (0.017-0.061)	0.043 (0.024-0.089)	0.048 (0.028-0.093)	0.063 (0.031-0.174)	0.080 (0.034-0.198)	<0.001

CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HMW, High molecular weight; hsCRP, high sensitivity C-reactive protein. Data presented are mean ± standard deviation. Data for triglycerides, fasting plasma glucose, immuno-reactive insulin, and HMW adiponectin, and hsCRP were skewed, and are presented as median (interquartile range) and were log-transformed for analysis. *P-value: ANOVA or X^2-test.

Table 3 Relationship between hsCRP and various characteristics according to gender

	Men, N = 822		Women, N = 1,097	
Characteristics	r (P-value)	β (P-value)	r (P-value)	β (P-value)
Age (years)	0.096 (0.006)	0.165 (<0.001)	0.202 (<0.001)	0.211 (<0.001)
Body mass index (kg/m^2)	0.188 (<0.001)	0.129 (0.002)	0.355 (<0.001)	0.245 (<0.001)
Smoking status, %	0.040 (0.249)	0.102 (0.005)	0.005 (0.863)	———
Alcohol consumption, %	-0.017 (0.637)	———	0.060 (0.008)	———
History of CVD, %	0.086 (0.013)	———	0.073 (0.016)	———
Systolic blood pressure (mmHg)	0.049 (0.164)	———	0.126 (<0.001)	-0.081 (0.009)
Diastolic blood pressure (mmHg)	0.028 (0.426)	———	0.103 (0.001)	———
Antihypertensive medication, %	0.115 (0.001)	———	0.138 (<0.001)	———
Triglycerides (mg/dL)	0.040 (0.257)	-0.099 (0.012)	0.209 (<0.001)	———
HDL cholesterol (mg/dL)	-0.190 (<0.001)	-0.152 (<0.001)	-0.196 (<0.001)	-0.061 (0.040)
LDL cholesterol (mg/dL)	0.028 (0.420)	———	0.179 (<0.001)	———
Antilipidemic medication, %	0.036 (0.301)	———	0.079 (0.009)	———
Serum uric acid (mg/dL)	0.126 (<0.001)	0.117 (0.001)	0.285 (<0.001)	0.164 (<0.001)
Fasting plasma glucose (mg/dL)	0.067 (0.056)	———	0.232 (<0.001)	0.121 (<0.001)
Immuno-reactive insulin (μU/mL)	0.162 (<0.001)	0.087 (0.010)	0.263 (<0.001)	———
Hypoglycemic medication, %	0.027 (0.445)	———	0.082 (0.007)	———
HMW adiponectin (μg/mL)	-0.094 (0.007)	———	-0.197 (<0.001)	-0.107 (0.001)
R^2	———	0.090 (<0.001)	———	0.227 (<0.001)

hsCRP, high sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HMW, High molecular weight. Data presented are mean ± standard deviation. Data for triglycerides, fasting plasma glucose, immuno-reactive insulin, and hsCRP were skewed and log-transformed for analysis. *r, Pearson's correlation coefficient; β, standard regression coefficient.

Table 4 Gender interaction between hsCRP and various subject characteristics

	N = 1,919
Characteristics	F (P-value)
Gender (men = 0, Women = 1)	4.573 (0.033)
Age (years)	68.24 (<0.001)
Body mass index (kg/m^2)	59.82 (<0.001)
Smoking status	1.925 (0.165)
Systolic blood pressure (mmHg)	4.839 (0.028)
Triglycerides (mg/dL)	1.452 (0.228)
HDL cholesterol (mg/dL)	12.82 (<0.001)
Serum uric acid (mg/dL)	38.38 (<0.001)
Fasting plasma glucose (mg/dL)	13.30 (<0.001)
Immuno-reactive insulin (μU/mL)	1.491 (0.222)
HMW adiponectin (μg/mL)	10.27 (0.001)
Gender *Smoking status	0.751 (0.386)
Gender *Systolic blood pressure	0.050 (0.823)
Gender *Triglycerides	0.845 (0.358)
Gender *Immuno-reactive insulin	0.056 (0.814)
Gender *Fasting plasma glucose	5.547 (0.019)
Gender *HMW adiponectin	1.709 (0.191)

hsCRP, high sensitivity C-reactive protein; HMW, high molecular weight. Data for hsCRP, triglycerides, fasting plasma glucose, immuno-reactive insulin, and HMW adiponectin were skewed and log-transformed for analysis.

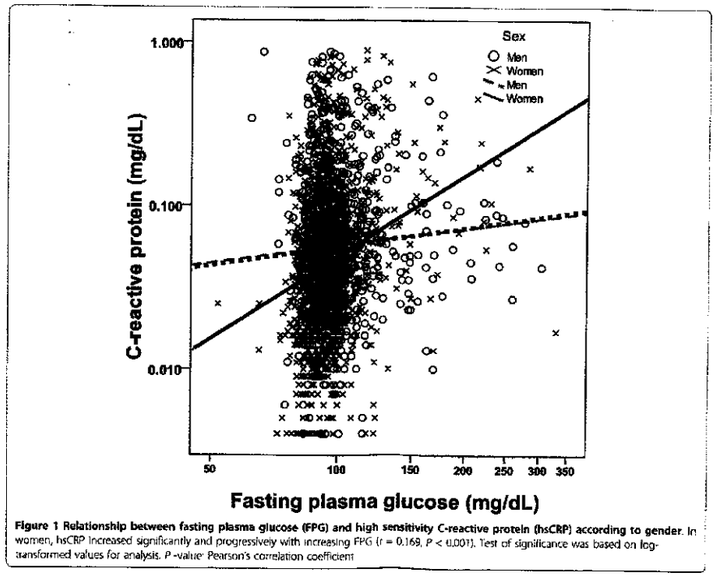

Figure 1 Relationship between fasting plasma glucose (FPG) and high sensitivity C-reactive protein (hsCRP) according to gender. In women, hsCRP increased significantly and progressively with increasing FPG ($r = 0.169$, $P < 0.001$). Test of significance was based on log-transformed values for analysis. *P-value: Pearson's correlation coefficient

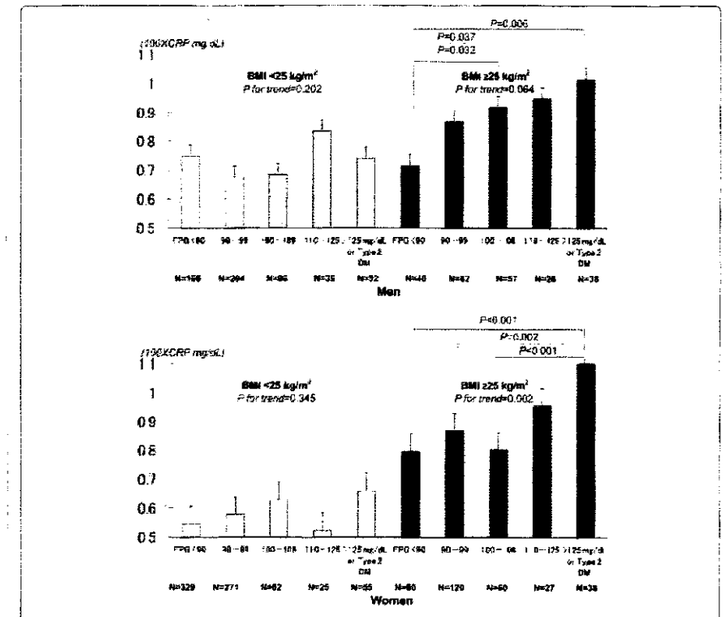

Figure 2 Geometric mean levels of high sensitivity C-reactive protein (hsCRP) and standard error bars, according to obesity, and fasting plasma glucose (FPG) category. Obesity was defined as a body mass index of ≥25 kg/m^2. hsCRP levels were adjusted for age, smoking status, systolic blood pressure, high-density lipoprotein cholesterol, uric acid, and high molecular weight (HMW) adiponectin. Data for HMW adiponectin and hsCRP were skewed, and log-transformed for analysis