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Plasma interleukin-1β concentrations are closely associated with fasting blood glucose levels in healthy and preclinical middle-aged nonoverweight and overweight Japanese men

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Abstract

Plasma interleukin (IL)-1β and IL-6 are markers that predict the risk of inflammation in diabetes. In the current study, we examined the relationship between fasting glucose and plasma inflammatory cytokines (IL-1β and IL-6) concentrations in healthy and preclinical middle-aged Japanese men (mean ± SD, 58.7 ± 7.8 years old) divided according to body mass index (<25 kg/m^2, nonoverweight group; ≥25 kg/m^2, overweight group). We conducted a cross-sectional study of 413 healthy and preclinical men aged 40 to 69 years who participated in health checkups in Japan. We measured their clinical parameters, lifestyle factors, and plasma IL-1β and IL-6 concentrations. Participants were classified according to their fasting blood glucose levels, and we compared their plasma cytokine levels. Plasma IL-1β and IL-6 levels in nonoverweight subjects were positively and strongly associated with fasting blood glucose and hemoglobin A_{1c}; in contrast, these cytokines were strongly associated with homeostasis model assessment of insulin resistance and fasting glucose in overweight subjects. Significant positive associations between plasma IL-1β and glucose concentrations were observed within the groups classified according to glucose concentrations, after adjustment for age and body mass index. The results of our current study show that plasma IL-1β levels are strongly associated with fasting blood glucose concentrations in healthy and preclinical nonoverweight and overweight Japanese men.

1. Introduction

Insulin resistance induces the development of diabetes and related complications such as cardiovascular disease, hypertension, and inflammation of peripheral tissues by impairing insulin action in various tissues [1-3]. In particular, insulin resistance and hyperglycemia, which are often associated with insulin resistance, increase the levels of plasma inflammatory cytokines. It has already been reported that insulin resistance and hyperglycemia in people with diabetes are associated with elevated plasma protein levels of circulating inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-12, IL-18, and tumor necrosis factor–α [4-6]. Among these cytokines, IL-1β and IL-6 in particular are thought to be important in predicting the risk of and the onset of diabetes [4]. It has been established that cytokines such as IL-1β induce apoptosis of islet β-cells and thus increase the risk of diabetes due to reduced insulin secretory capacity [7,8]. In addition, these cytokines induce macrophage infiltration into the vascular endothelium and increase the risk of atherosclerosis [9,10]. Of note, one of the major causes of insulin resistance is thought to be the production of cytokines, particularly IL-1β, IL-6, and tumor necrosis factor–α [11]. Although the functions of these cytokines are still under discussion, the results described above suggest that increased concentrations of these cytokines cause the development of diabetes, insulin resistance, and their complications.

Several epidemiologic studies in Western countries have documented that plasma IL-6 is positively associated with

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obesity and type 2 diabetes mellitus [4,12-14]. Although there are relatively few reports of IL-1β in Western countries, one study showed that plasma IL-1β protein levels are high in people with diabetes and obesity [4]. In addition, IL-1β expression in monocytes was found to increase after meals in overweight white women [15]. Because IL-1β is predominantly secreted from leukocytes, hyperglycemia may also induce IL-1β secretion into blood. However, particularly in Western people, it is difficult to delineate the effects of obesity (or insulin resistance) and hyperglycemia on IL-1β because hyperglycemia is strongly associated with obesity. In nonobese Japanese people with type 2 diabetes mellitus, plasma IL-6 concentrations are not associated with homeostasis model assessment of insulin resistance (HOMA-IR) [16], a marker for insulin resistance. In addition, Matsushita et al [17] reported that plasma IL-6 was not associated with the metabolic syndrome in Japanese men. These results indicate that these cytokines may not always be associated with markers for obesity or insulin resistance. In contrast to Western countries, it is known that the majority of diabetic patients in Japan are nonobese. Considering that Japanese people differ genetically and in lifestyle from Western people, it is important to investigate the association between these plasma inflammatory cytokines concentrations and blood parameters in nonoverweight and overweight Japanese people.

Therefore, in this study, we measured the plasma IL-1β and IL-6 concentrations in 413 Japanese subjects who were not taking medications for any metabolic disease.

2. Methods

2.1. Study population

We conducted a cross-sectional study of 413 healthy and preclinical men aged 40 to 69 years who participated in health checkups offered by the city government of Izunokuni (Shizuoka Prefecture, Japan) from June to September 2005. Anthropometric data and blood samples were collected from each participant by trained medical staff. Participants were also asked about their smoking status and self-reported physical activity. Smoking status was classified as never, past, or current; self-reported physical activity was classified as none, once a week, 2 to 3 times a week, or everyday. We excluded people who were being treated for stroke, hypertension, cardiac disease, diabetes, hyperlipidemia, liver disease, kidney disease, or gout. All subjects gave informed consent for the use of their personal information in this analysis. This study protocol was approved by the Ethics Committee of the University of Shizuoka, Shizuoka, Japan.

2.2. Measurements

Height, weight, fasting plasma glucose, triacylglycerol, total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured in the morning after an overnight fast. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Plasma samples were kept at −80°C for subsequent assays. Alcohol and energy intake during the preceding month was assessed with a brief self-administered diet history questionnaire (BDHQ) [18]. The plasma insulin levels were measured by a solid-phase 2-site enzyme immunoassay (Mercodia Ultrasensitive Insulin ELISA kit; Mercodia, Uppsala, Sweden). Plasma total adiponectin levels were measured by an enzyme-linked immunosorbent assay kit (Adiponectin ELISA kit; Otsuka Pharmaceutical, Tokyo, Japan). Plasma IL-1β and IL-6 levels were measured by enzyme-linked immunosorbent assays (Quantikine IL-1β or IL-6; R&D Systems, Oxford, United Kingdom).

The estimation of insulin resistance by HOMA-IR was calculated using the following formula: fasting blood glucose (milligrams per 100 milliliters) × fasting plasma glucose (milliunits per liter)/405.

Table 1
Physical characteristics, anthropometric and body composition measures, and lifestyle habits according to BMI of the 413 middle-aged men

	BMI <25	BMI ≥25	*P* value
n	309	104	
Age (y)	58.7 ± 8.0	58.7 ± 7.3	.584
BMI (kg/m^2)	22.1 ± 1.9	26.8 ± 1.5	<.001
Waist circumference (cm)	81.9 ± 6.1	92.4 ± 6.2	<.001
Energy intake (kcal/d)	2132 ± 509	2165 ± 559	.602
Smoking (%)[a]			
Never	105 (38.2)	37 (38.5)	.865
Current	99 (36.0)	32 (33.3)	
Past	71 (25.8)	27 (28.1)	
Self-reported physical activity (%)[a]			
Everyday	53 (19.3)	18 (18.8)	.999
2-3 times/wk	48 (17.5)	17 (17.7)	
Once/wk	36 (13.1)	13 (13.5)	
Never	137 (50)	48 (50)	
Alcohol intake (g/d)	30.3 ± 37.4	27.7 ± 37.4	.290
Systolic blood pressure (mm Hg)	125.0 ± 16.3	134.7 ± 17.1	<.001
Diastolic blood pressure (mm Hg)	75.8 ± 11.2	82.6 ± 12.4	<.001
Fasting blood glucose (mg/dL)[b]	101.9 ± 17.6	108.5 ± 31.7	<.001
HbA_{1c} (%)[c]	5.31 ± 0.96	5.26 ± 0.78	.531
Total cholesterol (mg/dL)	195.4 ± 30.4	202.4 ± 36.4	.078
HDL cholesterol (mg/dL)	55.5 ± 15.1	51.0 ± 14.5	<.01
Triacylglycerol (mg/dL)[b]	101 (70-146)	117 (83-168)	<.01
AST (U/L)	23.4 ± 11.0	24.3 ± 9.4	.076
ALT (U/L)	22.7 ± 13.6	29.3 ± 17.1	<.001
γ-GTP (U/L)	42.2 ± 77.5	48.2 ± 47.7	<.01
Creatinine (mg/dL)	0.803 ± 0.118	0.827 ± 0.123	.105
Insulin (mU/L)[b]	4.34 ± 5.02	7.65 ± 7.86	<.001
HOMA-IR[b,d]	1.12 ± 1.40	2.22 ± 2.98	<.001
Adiponectin (mg/L)	5.69 ± 3.15	4.82 ± 2.23	.053
IL-1β (pg/mL)	1.62 ± 2.39	2.50 ± 3.15	<.01
IL-6 (pg/mL)	3.01 ± 2.99	4.50 ± 3.76	<.01

Values are means ± SD for continuous variables and number of subjects (percentage) for categorical variables except for triacylglycerol (median [25-75%]). AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.

[a] 370 subjects due to missing values.

[b] Fasting samples only (n = 301, 100).

[c] 190 subjects due to missing values.

[d] HOMA-IR = fasting blood glucose × fasting insulin/405.

2.3. Statistical analysis

Overweight was defined for the Japanese population in accordance with the Japanese Society for the Study of Obesity as BMI of at least 25 kg/m^2. The clinical and biochemical data of the subjects are presented as means ± SD or as medians (and interquartile range) for variables with a skewed distribution, or as percentages. The means of 2 groups were compared with Mann-Whitney *U* test, and categorical data were compared using χ^2 test. Spearman rank correlation coefficient analysis was used to calculate correlations. Multiple linear regression analysis was performed to adjust for age and BMI. Mean values for clinical profiles according to fasting blood glucose were calculated after adjustment for age and BMI, and significant differences in mean values across fasting blood glucose levels were assessed using Dunnett test. For all analyses, a P value of < .05 was considered significant. All statistical analyses were performed using SPSS (Chicago, IL) software version 14.0 for Windows.

3. Results

The subjects studied were all healthy and preclinical Japanese men whose age ranged from 40 to 69 years (58.7 ± 7.8 years). The mean BMI was 23.3 ± 2.7 kg/m^2, and waist circumference was 84.5 ± 7.6 cm. The fasting blood glucose was 104 ± 22 mg/dL, and mean fasting plasma insulin was 5.17 ± 6.03 mU/L. The plasma adiponectin, IL-1β, and IL-6 concentrations were 5.47 ± 2.96 mg/L, 1.84 ± 2.62 pg/mL, and 3.39 ± 3.26 pg/mL, respectively.

Table 1 shows the clinical and lifestyle profiles in the nonoverweight (BMI, 15.5-24.9 kg/m^2) and overweight (BMI, 25.0-32.0 kg/m^2) groups. Compared with the nonoverweight group, the overweight group had significantly higher BMI, waist circumference, systolic and diastolic blood pressure, fasting blood glucose, triacylglycerol, insulin, HOMA-IR, alanine aminotransferase, γ-glutamyl transpeptidase (GTP), IL-1β, and IL-6 levels, and significantly lower HDL cholesterol. No significant difference was observed in age, hemoglobin A_{1c} (HbA_{1c}), total cholesterol, plasma adiponectin level, or energy intake between the 2 groups.

We next investigated the correlation between fasting plasma cytokine concentrations (IL-1β and IL-6) and clinical characteristics in the nonoverweight and overweight subjects (Table 2). Plasma IL-1β concentrations were strongly associated with plasma IL-6 concentrations (r = 0.758, P < .001) in all subjects. Plasma IL-1β and IL-6 levels were positively and strongly associated with fasting blood glucose and HbA_{1c} in all subjects. In nonoverweight subjects (ie, BMI <25 kg/m^2), plasma IL-1β and IL-6 levels were positively correlated with age, diastolic blood pressure, fasting blood glucose, and HbA_{1c}. Furthermore, IL-1β was positively correlated with fasting plasma insulin and HOMA-IR. In the overweight group, IL-1β and IL-6 levels were inversely associated with systolic blood pressure; but

Table 2
Correlation coefficients between inflammatory cytokines and anthropometric measurements and blood parameters

	IL-1β (pg/mL)			IL-6 (pg/mL)		
	All n = 398	BMI <25 n = 301	BMI ≥25 n = 97	All n = 321	BMI <25 n = 239	BMI ≥25 n = 82
IL-1β (pg/mL)				0.758‡	0.716‡	0.844‡
IL-6 (pg/mL)	0.758‡	0.716‡	0.844‡			
Age (y)	0.154†	0.159†	0.159	0.173†	0.213‡	0.064
BMI (kg/m^2)	0.138†	0.070	−0.030	0.142*	0.026	−0.120
Waist circumference(cm)	0.117*	0.073	−0.021	0.086	−0.026	−0.055
Systolic blood pressure (mm Hg)	−0.007	0.031	−0.227*	0.080	0.144*	−0.249*
Diastolic blood pressure (mm Hg)	0.096	0.137*	−0.116	0.170*	0.200†	−0.027
Fasting blood glucose (mg/dL)	0.344‡	0.301‡	0.435‡	0.287‡	0.256‡	0.288†
HbA_{1c} (%)[a]	0.232†	0.256†	0.171	0.357‡	0.417‡	0.161
Total cholesterol (mg/dL)	−0.074	−0.076	−0.107	−0.063	−0.046	−0.106
Triacylglycerol (mg/dL)	0.086	0.055	0.114	0.130*	0.111	0.065
HDL cholesterol (mg/dL)	−0.111*	−0.077	−0.147	−0.119*	−0.103	−0.083
AST (U/L)	0.184‡	0.145*	0.307†	0.131*	0.051	0.357†
ALT (U/L)	0.018	−0.059	0.159	0.029	−0.077	0.212
γ-GTP (U/L)	0.424‡	0.423‡	0.385‡	0.418‡	0.375‡	0.450‡
Creatinine (mg/dL)	−0.044	−0.064	−0.005	−0.150†	−0.184†	−0.067
Insulin (mU/L)	0.196‡	0.128*	0.245*	0.169†	0.079	0.241*
HOMA-IR	0.235‡	0.170†	0.300†	0.206‡	0.125	0.270*
Adiponectin (mg/L)	0.035	0.092	−0.078	−0.026	0.048	−0.160
Alcohol intake (g/d)	−0.044	−0.020	−0.108	−0.090	−0.073	−0.119

[a] 190 subjects due to missing values.
* P < .05 by Spearman correlation coefficient.
† P < .01 by Spearman correlation coefficient.
‡ P < .001 by Spearman correlation coefficient.

they were positively associated with fasting blood glucose, plasma insulin level, and HOMA-IR. Interleukin-1β and IL-6 were not associated with adiponectin in either the nonoverweight or overweight groups. Aspartate aminotransferase was positively associated with IL-1β levels in both groups and was associated with IL-6 levels in the overweight group. γ-Glutamyl transpeptidase was positively associated with the levels of both cytokines in both groups. Significant associations between creatinine and these cytokine levels were only observed for IL-6 in overweight subjects.

Alcohol intake (Table 2) and smoking (data not shown) were not associated with plasma cytokine concentrations of IL-1β and IL-6. Self-reported physical activity was positively associated with IL-1β in the full study population (everyday, 2.62 ± 3.29 pg/mL; 2-3 times a week, 1.76 ± 2.52 pg/mL; once a week, 2.19 ± 2.77 pg/mL; never, 1.46 ± 2.30 pg/mL; P = .13). However, this association disappeared when the subjects were divided into the nonoverweight and overweight groups. IL-1β tended to be associated with self-reported physical activity in the nonoverweight group (nonoverweight group: everyday, 2.23 ± 3.16 pg/mL; 2-3 times a week, 1.46 ± 2.11 pg/mL; once a week, 2.05 ± 2.53 pg/mL; never, 1.29 ± 2.06; P = .066; overweight group: everyday, 3.77 ± 3.48 pg/mL, 2-3 times a week, 2.67 ± 3.43 pg/mL; once a week, 2.65 ± 3.54 pg/mL; never, 1.93 ± 2.85 pg/mL; P = .225). IL-6 was not associated with self-reported physical activity in the full study population or in the nonoverweight and overweight groups of subjects (data not shown).

To confirm the correlation between glucose and plasma cytokine concentrations, we divided the nonoverweight subjects into 4 groups based on fasting blood glucose concentrations (<89, 90-99, 100-109, and 110-125 mg/dL), as shown in Table 3. We also divided the overweight subjects into groups based on fasting blood glucose concentrations, although these subjects were divided into 3 groups (<99, 100-109, and 110-125 mg/dL) because the number of subjects with fasting blood glucose less than 89 mg/dL was too small for meaningful comparisons (n = 9); therefore, these subjects were grouped with those with fasting blood glucose levels of 80 to 99 mg/100 mL. We also excluded people with fasting blood glucose of at least 126 mg/dL and those who were diagnosed with diabetes because of the small number of subjects in both groups. After adjustment for age and BMI, those with preclinical hyperglycemia (110-125 mg/dL) had higher systolic and diastolic blood pressure and a higher IL-1β level than those with the lowest fasting blood level (<89 mg/dL) in the

Table 3
Characteristics of the subjects according to fasting blood glucose level adjusted for age and BMI (except for fasting blood glucose)

		<89 mg/dL	90-99 mg/dL	100-109 mg/dL	110-125 mg/dL
BMI <25	Fasting blood glucose (mg/dL)	85.4 ± 3.3	95.2 ± 2.9	103.6 ± 2.7	115.5 ± 4.8
	n	50	114	84	35
	Waist circumference (cm)	84.1 ± 4.0	85.0 ± 4.8	83.9 ± 3.9	84.8 ± 3.7
	Systolic blood pressure (mm Hg)	125.5 ± 17.9	124.7 ± 15.7	127.0 ± 15.7	132.2 ± 11.5
	Diastolic blood pressure (mm Hg)	75.0 ± 13.1	76.1 ± 11.4	77.9 ± 9.3	81.6 ± 9.1*
	Total cholesterol (mg/dL)	194.0 ± 26.7	197.5 ± 29.5	197.7 ± 32.6	203.1 ± 33.9
	HDL cholesterol (mg/dL)	54.9 ± 15.5	52.9 ± 13.6	54.2 ± 15.1	54.2 ± 12.6
	Insulin (mU/L)	3.97 ± 2.68	5.14 ± 5.22	4.76 ± 3.64	6.71 ± 7.42
	HOMA-IR	0.92 ± 0.55	1.28 ± 1.24	1.26 ± 0.92	1.91 ± 2.08
	Adiponectin (mg/L)	5.02 ± 2.85	5.32 ± 2.61	5.42 ± 2.86	4.94 ± 2.90
	IL-1β (pg/mL)	0.84 ± 1.19	1.67 ± 2.34*	2.26 ± 2.51‡	2.67 ± 2.90†
	IL-6 (pg/mL)	2.32 ± 2.40	3.18 ± 2.91	3.68 ± 2.97	3.53 ± 3.13
		<99 mg/dL		100-109 mg/dL	110-125 mg/dL
BMI ≥25	Fasting blood glucose (mg/dL)	92.5 ± 4.5		104.2 ± 2.8	115.0 ± 4.2
	n	32		40	22
	Waist circumference (cm)	84.3 ± 5.7		85.4 ± 5.4	82.5 ± 3.5
	Systolic blood pressure (mm Hg)	130.3 ± 19.4		125.1 ± 17.1	128.9 ± 15.8
	Diastolic blood pressure (mm Hg)	79.2 ± 14.8		75.3 ± 11.1	79.3 ± 12.5
	Total cholesterol (mg/dL)	195.2 ± 38.0		195.5 ± 40.4	189.4 ± 26.2
	HDL cholesterol (mg/dL)	56.9 ± 16.1		59.6 ± 15.4	51.0 ± 8.8
	Insulin (mU/L)	2.70 ± 2.84		6.93 ± 10.97	4.45 ± 3.58
	HOMA-IR	0.42 ± 0.65		1.65 ± 2.77*	1.18 ± 0.98*
	Adiponectin (mg/L)	5.25 ± 2.35		6.72 ± 2.25	5.48 ± 2.26
	IL-1β (pg/mL)	0.41 ± 1.90		1.91 ± 2.75*	4.01 ± 3.85†
	IL-6 (pg/mL)	2.63 ± 3.56		3.91 ± 3.23	5.07 ± 4.51

Fasting samples only (n = 401). Data are expressed as means ± SD.
Significantly different from the group of lowest fasting blood glucose:
* $P < .05$.
† $P < .01$.
‡ $P < .001$.

nonoverweight subjects (Table 3). On the other hand, among the overweight subjects, those with preclinical hyperglycemia (110-125 mg/dL) had higher IL-1β levels and HOMA-IR. Plasma IL-1β levels increased with increasing glucose concentrations in both groups. In nonoverweight subjects, significant differences in plasma IL-1β concentrations were observed between those with the lowest fasting glucose concentration (<89 mg/dL) and those with higher fasting blood glucose levels (90-99 mg/dL: 2.0-fold, $P < .05$; 100-109 mg/dL: 2.7-fold, $P < .001$; 110-125 mg/dL: 3.2-fold, $P < .01$). Similarly, in overweight subjects, significant differences in plasma IL-1β concentrations were observed between those with the lowest fasting blood glucose levels (<99 mg/dL) and those with higher fasting blood glucose levels (100-109 mg/dL: 4.7-fold, $P < .05$; 110-125 mg/dL: 9.8-fold, $P < .01$). The plasma IL-6 concentrations tended to be elevated in subjects with increasing glucose concentrations in the nonoverweight and overweight groups of subjects, but this was not significant (Table 3).

4. Discussion

In this study, we focused on the relationship between interleukins (IL-1β and IL-6) and metabolic risk factors in Japanese middle-aged men. As shown in Table 1, the plasma levels of IL-1β and IL-6 were more strongly associated with markers for hyperglycemia such as fasting blood glucose and HbA_{1c} than with markers for obesity such as BMI and waist circumference in healthy and preclinical Japanese men. It has been reported in a number of studies based in Western countries that plasma IL-6 levels are associated with BMI, waist circumference, and HOMA-IR [4,19,20]. Haffner et al [19] reported that IL-6 levels are associated with BMI and insulin resistance in obese type 2 diabetes mellitus patients. It was reported that obese white persons with diabetes have elevated IL-6 levels and that an association was seen between a combined increase in plasma IL-1β and IL-6 levels and an increased risk of developing type 2 diabetes mellitus [4]. The results obtained in our study are not consistent with the results in Western countries (Table 2). Previous studies have shown that Japanese people tend to develop diabetes without being overweight and that IL-6 is not always associated with obesity or insulin resistance [16,17]. Thus, it is likely that the associations between these cytokines and BMI are weaker in Japanese populations than in populations in Western countries. Therefore, we hypothesized that the levels of these cytokines may be independently associated with indices of hyperglycemia in nonoverweight subjects.

To examine this hypothesis, we divided the subjects into 2 groups based on their BMI; those with BMI less than 25 kg/m^2 were classified as nonoverweight subjects, whereas those with BMI of at least 25 kg/m^2 were classified as overweight subjects according to the Japanese Society for the Study of Obesity guidelines (Table 2). In the overweight subjects, we found a positive correlation between IL-1β or IL-6 and markers of insulin resistance such as insulin and HOMA-IR, in addition to fasting glucose. These results are consistent with the results reported in Western countries [21,22]. It has been reported that IL-6 production from adipose tissues could explain 10% to 30% of the total circulating IL-6 concentration in humans [23]. In addition, IL-1β is thought to be elevated in leukocytes by hyperglycemia caused by insulin resistance. Thus, some of the increase in plasma IL-6 and IL-1β concentrations in overweight Japanese subjects may be due to insulin resistance and/or hyperglycemia caused by insulin resistance. Interestingly, we found a positive association in nonoverweight subjects between these cytokines and markers for hyperglycemia (fasting glucose and HbA_{1c}) (Table 2). After classifying the subjects into 4 (nonoverweight subjects) or 3 (overweight subjects) groups according to fasting blood glucose concentrations, we compared parameters after adjustment for age and BMI. In this analysis, the plasma IL-1β levels in nonoverweight subjects were strongly and independently associated with hyperglycemia, but less strongly with HOMA-IR, whereas plasma IL-1β levels in overweight subjects were strongly associated with HOMA-IR and hyperglycemia (Table 3). These results suggest that plasma IL-1β levels are strongly associated with increasing fasting blood glucose concentrations in healthy and preclinical nonoverweight subjects. It has been reported that IL-1β induces apoptosis of islet β-cells [8,24] and that antagonism of IL-1β by IL-1 receptor antagonists inhibits apoptosis of β-cells and maintains insulin secretion from β-cells [25]. Treatment of diabetic patients with anakinra, a recombinant human IL-1 receptor antagonist, improved glycemic status, maintained high C-peptide secretion, and reduced plasma IL-6 levels [26,27]. These findings indicate that IL-1β is closely associated with β-cell dysfunction. Thus, the association between fasting blood glucose and the plasma concentrations of IL-1β and IL-6 in this study of nonoverweight and overweight Japanese men may be due to β-cell dysfunction and the loss of insulin secretion. This suggests that Japanese men tend to develop diabetes through impaired pancreatic β-cell function, without developing overweight or obesity.

The mechanism involved in the association between plasma IL-1β protein concentration and elevated fasting glucose levels in Japanese healthy and preclinical men is still unknown. It is known that most of the IL-1β messenger RNA (mRNA) is degraded without significant elongation of the protein when IL-1β mRNA assembles into a large polyribosome. IL-1β protein in monocytes is translated from the mRNA by stimulation of Toll-like receptor ligands or by IL-1 itself. The translated protein is the precursor IL-1β that is an inactive form located in the cytosol, and the precursor is cleaved by caspase-1 to form active IL-1β and is secreted [28]. Our recent studies have demonstrated that constant hyperglycemia and intermittent postprandial hyperglycemia in rats induced mRNA levels of IL-1β in peripheral leukocytes [29-31]. In addition, a recent cell study has

shown that human monocytic THP-1 cells exposed to high glucose produced IL-1β mRNA and protein, and secreted active IL-1β protein [32]. One of the causes of the higher concentration of secreted active IL-1β in plasma in healthy and preclinical Japanese men with higher fasting glucose level in the current study may be the increased mRNA and protein levels of IL-1β in leukocytes. In addition, it should be noted that the IL-1β concentration reported in this study is likely to be underestimated because the concentration of IL-1β was found to be much higher when it is stabilized by injecting healthy subjects and patients with cryopyrin-associated periodic syndromes with an antibody to IL-1β [33]. Thus, further studies are needed to investigate the association between fasting glucose concentration and stabilized active IL-1β in plasma, and the mRNA and immature protein levels of IL-1β in peripheral leukocytes such as monocytes, neutrophil, and T lymphocytes.

The lifestyle factors that contributed to the circulating concentrations of IL-1 β and IL-6 in the Japanese men in the current study remain unknown. It was reported that plasma IL-1β levels were increased by the intake of oats, wheat bread, and potato, food items with high glycemic indices, compared with the intake of rye bread and pasta, which have low glycemic indices, for 12 weeks in 47 overweight men and women in Finland [34]. In addition, studies in Western countries have shown that higher fiber intake was associated with lower plasma IL-6 concentrations [35,36]. These results indicate that the intake of foods that cause marked postprandial hyperglycemia can increase plasma IL-1β and IL-6 levels. In addition, it is known that dietary intake differs greatly between Western countries and Japan. It has been reported that the intake of a Western-style diet, which includes higher amounts of red and processed meats, sweets, desserts, potato chips, and refined grains, substantially increases the plasma IL-6 concentration, compared with that of a diet based on higher intake of fruits, vegetables, legumes, fish, poultry, and whole grains [37]. Thus, it is likely that differences in dietary intake may affect plasma cytokine concentrations in Japanese men differently from Western men. In this study, we assessed dietary intake by a BDHQ [18]. Unfortunately, we did not find any significant associations between dietary intake and plasma cytokine levels in plasma in nonoverweight and overweight subjects (data not shown). Nevertheless, because the population is relatively small, studies of larger populations are needed to confirm the association between dietary intake and plasma cytokine levels in overweight and nonoverweight Japanese individuals.

In summary, in healthy and preclinical Japanese men, high plasma levels of IL-1β and IL-6 were positively associated with hyperglycemia rather than markers of obesity such as BMI or waist circumference. The results of the present study suggest that plasma levels of IL-1β are associated with increased fasting blood glucose levels in healthy and preclinical nonoverweight and overweight Japanese subjects.

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