Elevated C-Reactive Protein, Abdominal Obesity, and Glucose Tolerance Status in Japanese-Brazilians

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Abstract: Although evidences indicate that C-reactive protein (CRP) levels are independent predictors of type 2 diabetes (DM), some studies either did not support this association or examine it extensively throughout the stages of glucose tolerance. In a cross-sectional population-based survey, we investigated the relation between CRP and the risk of newly diagnosed impaired glucose tolerance (IGT), and DM among Japanese-Brazilians (374 men and 464 women). In age-gender–adjusted analyses, the risks of IGT and type 2 diabetes were significantly higher in the highest CRP tertile as compared with participants with a normal glucose tolerance status (*P* for trend = 0.0001 in both conditions). After further adjustments for confounding factors, including waist circumference, only the odds of having IGT in the highest CRP tertile was still significant (odds ratio 1.87 [95% CI 1.04–3.37). Our results suggest that low-grade inflammation increases the risk of IGT in Japanese-Brazilians but that some of the risk is confounded by abdominal adiposity.

Keywords: C-reactive protein, insulin resistance, IGT, type 2 diabetes, abdominal obesity.

INTRODUCTION

An accumulating body of evidence indicates that ongoing low-grade inflammation may play an intermediary role in the pathogenesis of type 2 diabetes and that inflammatory cytokines secreted by adipose tissue in general and visceral adiposity in particular may exert an endocrine effect that confers insulin resistance [1,2]. Recent epidemiologic studies have demonstrated associations of elevated serum levels of C-reactive protein (CRP) with obesity, visceral adiposity, and insulin resistance, suggesting that a chronic inflammatory state is associated with hyperglycemia and diabetes through obesity or increased insulin resistance [3-7]. Although substantial evidence indicates that serum CRP levels are independent predictors of the development of type 2 diabetes [7-11], some studies either did not support this association [12-13] or examine it extensively throughout the stages of glucose tolerance.

Prevalence of glucose tolerance disturbances have been escalating throughout the world and the highest rates have been reported among populations who have undergone rapid changes in their lifestyle, such as Pima Indians and Japanese-Brazilians [14-15]. This could reflect the strong genetic susceptibility associated with the adoption of unfavorable environmental conditions.

Japanese subjects have been characterized by greater visceral adiposity at lower body mass index (BMI) values and lower CRP concentrations than that in westerners. Previous reports on Japanese-Americans [10] and in a general Japanese population [11] suggested that elevated CRP concentration is a significant predictor of diabetes independent of obesity and insulin resistance. However, neither of these studies controlled for the effect of measures of abdominal obesity, without any information about whether a pro-inflammatory state is present in individuals with impaired glucose tolerance. High age-adjusted prevalence rates of type 2 diabetes and associated diseases have been reported in Japanese-Brazilians, with abdominal obesity, physical inactivity, and high dietary intakes of refined cereals among the main risk factors for glucose disturbances [16]. In the present cross-sectional population-based study, we therefore examined the relationship between high-sensitivity serum CRP levels and the risk of newly diagnosed impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes among Japanese-Brazilians living in Bauru, southeast Brazil.

METHODS

Study Population

The Japanese-Brazilian Diabetes Study investigates the prevalence and incidence of diabetes and related diseases in

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a population of Japanese ancestry living in Bauru, São Paulo State, Brazil. In 1993, a cross-sectional population-based study was conducted on a representative sample of Japanese-Brazilian subjects living in Bauru to estimate the prevalence of diabetes type 2 and associated diseases. At that time, 647 subjects of Japanese ancestry, aged 40–79 years, either Japan-born (first generation, 37·3 %) or Brazil-born (second generation, 62·7 %) were included. In 1999, a second survey was carried out following the same protocol, except that dietary patterns were assessed using a validated food-frequency questionnaire developed for Japanese-Brazilian subjects. In addition to the participants enrolled in the first survey, the whole Japanese-Brazilian population over 30 years of age was invited to participate (1751 subjects). Data collection from 1330 subjects was completed in December 2000. A total of 394 individuals studied in 1993 (60.9 %) participated in the second survey. Of the study sample in 1993, sixty-nine subjects (10.6 %) had died, fifty-seven (8.7 %) had moved and 127 (19.7 %) refused to participate. Among the new participants in the second survey (n = 1104), the proportion of non-responders was 15.2 % (n = 168), including twenty-three deaths (2.1 %) that occurred after the beginning of data collection. Data collected from 1,283 first- (Japan-born) and second-generation (Brazil-born) subjects were available (Fig. **1**) [15,17]. After exclusion of subjects who self-reported glucose disturbances whose treatment could affect the CRP concentrations, and/or had CRP concentrations higher than or equal to 1 mg/dl, the remaining 838 participants (374 men and 464 women) were considered for the present analyses (Fig. **1**).

Questionnaire

Assessments of medical history and medications, smoking, alcohol intake, socioeconomic status and practice of leisure-time physical activities have been described previously [15,17]. Participants were interviewed at home by trained personnel and scheduled for the clinical examination in an outpatient clinic. Food consumption was assessed using a food frequency questionnaire developed and validated for the Japanese-Brazilian community as described previously [18]. Information on smoking status (never, past, or current) and drinking habits was obtained with a structured questionnaire.

Clinical Investigations

Height, weight, and waist circumference were measured with the subjects standing. BMI (kg/m^2) was calculated. Waist circumference was measured at the level of the umbilicus, and abdominal obesity was defined as a waist circumference ≥ 0.90 m for men and ≥ 0.80 m for women. Throughout the study all body measurements were made according to standard protocols and cut-offs proposed by the WHO for Asians [19]. The last two of three measures of

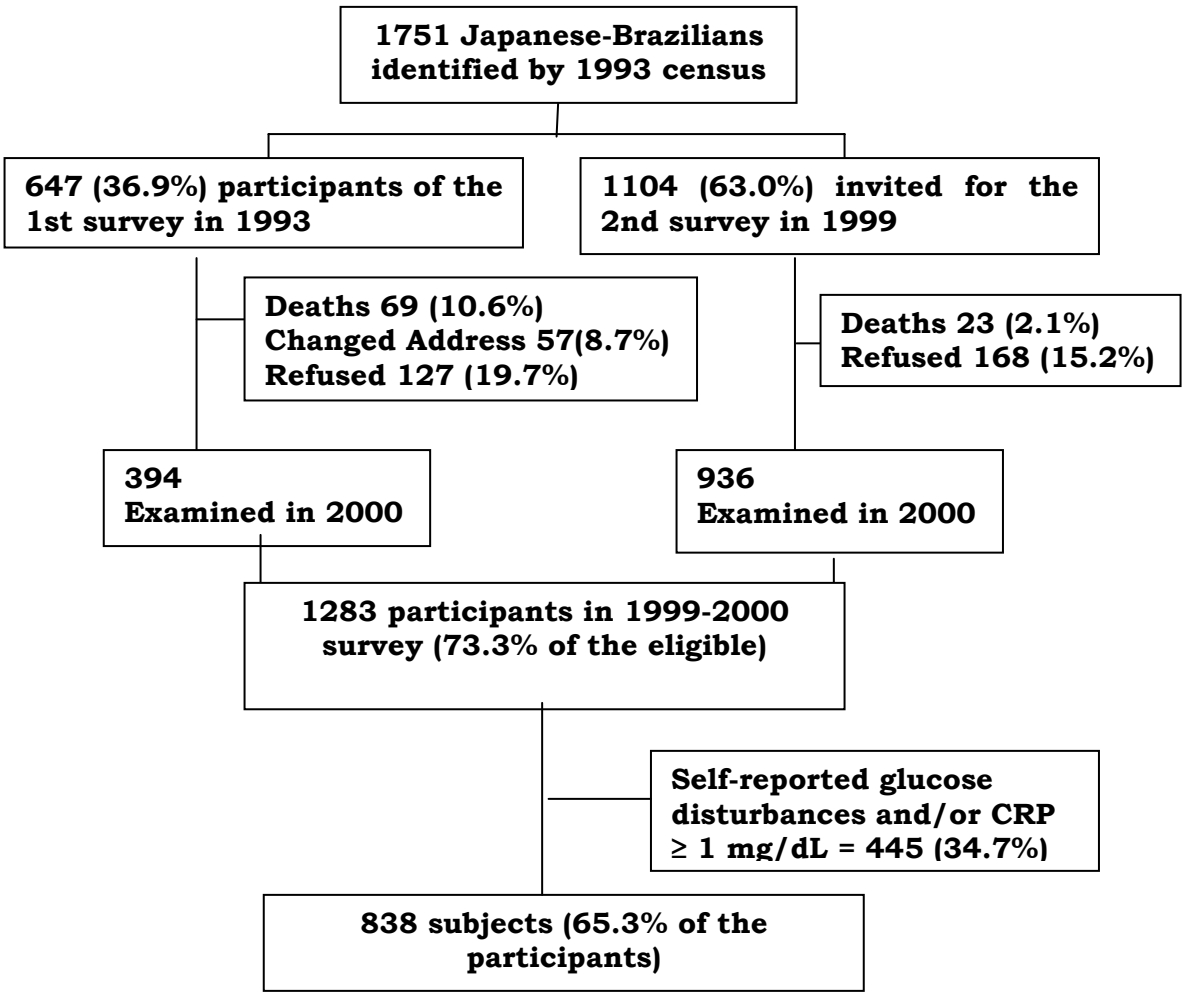

Fig. (1). Sampling strategies and participation to the first (1993) and second (1999-2000) cross-sectional surveys, and the final sample for the present study.

blood pressure obtained with an automatic device were considered (Omron model HEM–712 C, Omron Health Care, USA).

Biochemical Measurements

Blood samples were obtained after a 10-hour overnight fast, and the serum was frozen at −20°C immediately after collection. Total cholesterol, HDL cholesterol, and triacylglycerol were all measured enzymatically. Plasma glucose was determined by the glucose-oxidase method. Insulin concentrations were determined by a monoclonal antibody–based immunofluorimetric assay (AutoDelfia; Perkin Elmer Life Sciences, Norton, OH, USA). Coefficients of variation were less than 10% for all assays. High-sensitivity CRP levels were determined by a chemiluminescent immunometric assay (Immulite High Sensitivity CRP Assay; DPC, Los Angeles, CA, USA). To limit confounding of the results due to acute infection or diseases associated with hypersedimentation, we excluded participants with CRP concentrations higher than or equal to 1.0 mg/dl [20].

Classification Criteria

Subjects underwent a standard 75-g oral glucose tolerance test according to WHO recommendations. WHO criteria for diabetes (fasting plasma glucose ≥ 126 mg/dl or 2-h glucose ≥ 200 mg/dl), IFG (fasting plasma glucose levels 110–126 mg/dl) and IGT (2-h plasma glucose levels 140–200 mg/dl) were used to classify subjects [21]. Homeostasis model assessment index was calculated to estimate insulin resistance (HOMA-IR = fasting glucose x fasting insulin/22.5) [22]. Subjects with serum levels of total cholesterol ≥ 200 mg/dl; LDL-cholesterol ≥ 130 mg/dl; triacylglycerol ≥ 150 mg/dl, or HDL-cholesterol ≤ 40 mg/dl and/or current treatment with antilipidemic drugs were classified as dyslipidemic [23]. Hypertension was defined as a systolic and/or diastolic blood pressure ≥ 140/90 mmHg and/or current treatment with antihypertensive agents [24].

Statistical Methods

Statistical analyses were performed with the software SPSS 12.0. A two-sided $P < 0.05$ was considered statistically significant. Differences in means, medians, and proportions of confounding factors across the CRP categories were tested by one-way ANOVA, the Kruskal-Wallis test, and the chi-square test, respectively. Variables with skewed distributions (all biochemical indicators) were transformed using their natural logarithms. We used linear regression analysis to examine associations between CRP levels and markers of glucose metabolism and insulin sensitivity. Regression coefficients were calculated using the log-transformed CRP values divided by its standard deviation as dependent variable. Logistic regression models were used to calculate the odds ratio (ORs) and their 95% CIs for IFG, IGT, and type 2 diabetes as three separate outcomes compared with normal glucose tolerance status, with individuals in the lowest tertile category of CRP concentrations as the referent category. ORs were adjusted for gender, age (years), generation (first- and second-generation), smoking (never, past, current smokers), hypertension (yes/no), dyslipidemia (yes/no), practice of leisure-time physical activity (yes/no), alcohol beverages (never, 0.2–54.0, > 54 g/day), total energy intake, dietary fiber, BMI, waist circumference (cm), HOMA-IR, and possible interactions. To assess trends across tertile categories, we assigned the median value of each tertile category to individuals with CRP levels in the category and then included this tertile median variable as a continuous factor in the logistic regression models. The P for linear trend was the resulting P-value for the associated logistic regression coefficient.

RESULTS

The characteristics of the study population across CRP tertiles are shown in Table **1**. Participants with higher levels of CRP were older, were heavier, tended to consume less alcohol, and were less likely to participate in physical exercise during leisure time. The frequencies of abdominal obesity, hypertension, and dyslipidemia increased across the highest CRP levels. Among the 838 participants, there were 194 (23%) newly diagnosed cases of IFG, 217 (26%) of IGT (77 with isolated IGT and 140 with IGT+IFG), and 202 (25%) of type 2 diabetes. The frequency of abdominal obesity, hypertension, and dyslipidemia increased throughout glucose tolerance status from normal to type 2 diabetes (Table **2**).

In all participants, BMI, waist circumference, fasting and post-load plasma glucose and insulin (2-h glucose and 2-h insulin, respectively), and HOMA-IR were significantly correlated with CRP concentrations in age-gender adjusted models. However, in multiple-adjusted linear models, only markers of insulin resistance (2-h glucose and HOMA-IR), BMI, and waist circumference were correlated with CRP values (Table **3**). In stratified analyses according to abdominal obesity status, only 2-h glucose levels were correlated with CRP concentrations independent of abdominal obesity, using the same multiple-adjusted models (regression coefficients and 95% CI): 0.259 (0.006, 0.513; $P = 0.045$) for normal waist, and 0.542 (0.152, 0.931; $P = 0.007$) for abdominal obesity.

The ORs of glucose tolerance disturbances according to tertile of CRP are shown in Table **4**. Comparing with participants with normal glucose tolerance, CRP was not associated with IFG. After multiple adjustments, subjects in the highest CRP tertile had higher odds of having IGT. The strong association between elevated CRP and IGT remained after additional adjustment for waist circumference and HOMA-IR. However, CRP was not independently associated with type 2 diabetes. Additional adjustment for BMI weakened the association between CRP and IGT [OR (95%CI) = 1.23 (0.73–2.09) and 1.78 (1.02–3.18) for CRP tertiles 2 and 3, respectively; p for trend = 0.049]. There was no evidence of any interaction.

DISCUSSION

In this population-based cross-sectional study among Japanese-Brazilians, higher levels of CRP were associated with IGT, independent of well-known risk factors such as abdominal adiposity and insulin resistance. Adjustment for BMI, waist circumference, or HOMA-IR (a surrogate for insulin resistance) markedly attenuated these associations. Since adipose tissue is a major source of pro-inflammatory

Table 1. Characteristics of the Japanese-Brazilians According to Tertiles of Serum High-Sensitivity CRP Levels

	High-Sensitivity CRP Level (mg/dl)		
	0.001–0.068	**0.069-0–177**	**0.179–0.965**
n	287	289	262
Gender (% male)	44.6	48.8	40.3
Generation (% first-/second-)	17/83	20/80	14/86
Age in years (S.D.)*	54 (13)	56 (12)	57 (11)
BMI (S.D.)	22.8 (2.9)	24.8 (3.2)	26.4 (4.3)
Mean waist circumference (S.D.)			
Men	83.6 (8.4)	88.4 (8.6)	91.6 (11.0)
Women	74.3 (6.8)	79.5 (8.0)	83.7 (9.4)
Cigarette smoking (%)*			
Never	73.0	66.7	73.3
Past	13.7	17.9	16.0
Current	13.3	15.4	10.8
Intake of alcohol beverages (%)*			
Never	57.1	54.3	65.2
0.2–54.0 g/day	23.0	23.9	15.5
> 54.0 g/day	19.9	21.8	19.3
Abdominal obesity (%)*	18.1	43.9	61.7
Hypertension (%)*	23.7	44.3	51.0
Dyslipidemia (%)*	78.4	89.6	90.3
Practice of leisure time physical activity (%)*	19.9	14.5	12.4
Dietary intakes			
Total energy (kcal/day)	1932 (1579–2332)	2046(1628–2023)	1900 (1544–1900)
Total fat (% energy/day)	32 (29–37)	32 (29–37)	33 (28–37)
Saturated fat (g/day)	16 (13–22)	17 (12–22)	16 (12–21)
Total fiber (g/day)	15 (12–21)	17 (13–22)	16 (12–21)

Data are means ± SD or medians (interquartile ranges) unless otherwise indicated.
*$p<0.05$.

cytokines and greater visceral adiposity in Japanese descendants increases the risk of IGT at low BMI values [25], it is to be expected that abdominal adiposity weakens the association between CRP, IGT, and type 2 diabetes. This could explain why this attenuation effect was stronger on the association between CRP and type 2 diabetes, since newly diagnosed diabetic patients had higher proportion of abdominal obesity in this study.

Previous research on the association between CRP, obesity, and disturbances in glucose tolerance has been inconclusive. The Third National Health and Nutrition Examination Survey (NHANES III) found higher CRP levels in subjects with type 2 diabetes than in those without diabetes or those with IFG. Compared with participants with normal fasting glucose levels, participants with IFG and newly diagnosed diabetes had 0.99 (95% CI 0.72–1.37), and 1.84 (1.25–2.71) odds of having an elevated CRP concentration after adjustment for age, sex, race or ethnicity, education, and BMI. However, this cross-sectional analysis neither included IGT condition nor controlled for the effect of measures of abdominal obesity and/or insulin resistance [3]. On the other hand, the Hong Kong Cardiovascular Risk Factors Prevalence Study found that CRP predicts the risk of remaining in IGT or progressing to diabetes in Chinese subjects with IGT, after adjusting for BMI and waist circumference. Unfortunately, measures of insulin resistance were not considered in the analyses [26]. In prospective studies among Japanese-Americans [10] and in a general Japanese population [11], CRP was a risk factor for development of type 2 diabetes, independent of either obesity or insulin resistance. However, these studies did not include measures of abdominal obesity or individuals with IGT.

A body of evidence reinforces the concept that obesity (particularly centrally) is an inflammatory state: plasma concentrations of TNF-α, IL-6 (which also promotes the production of CRP), CRP, and other inflammatory mediators have

Table 2. Characteristics of the Japanese-Brazilians According to Glucose Tolerance Status

	Glucose Tolerance Status			Type 2 Diabetes (n=202)
	Normal (n= 225)	IFG (n=194)	IGT (n=197)	
Gender (%male)*	33	52	43	51
Generation (%first-/second-)	18/82	17/83	21/79	12/88
Mean age (SD)**	52 (14)	55 (13)	58 (12)	58 (11)
Mean BMI (SD)**	23.0 (2.9)	24.0 (3.5)	25.2 (4.0)	26.5 (3.9)
Mean waist circumference (SD)				
Men**	83.3 (6.8)	86.1 (9.1)	89.1 (10.0)	91.1 (10.7)
Women**	75.6 (7.5)	77.6 (8.6)	80.9 (9.6)	84.2 (8.3)
Cigarette smoking (%)*				
Never	74.3	63.3	72.6	72.6
Ex	9.7	17.3	19.7	17.0
Current	15.9	19.4	7.6	10.4
Intake of alcohol beverages (g/day)*				
Never	61.8	57.9	54.9	61.2
0.2- 54.0	21.9	21.8	25.7	13.1
> 54.0	16.2	20.3	19.5	25.7
Abdominal obesity (%)*	22.8	31.0	50.4	61.2
Hypertension (%)*	25.0	37.1	44.7	52.8
Dyslipidaemia (%)*	77.2	83.8	89.4	94.4
Practice of leisure time physical activity (%)*	15.4	17.3	15.5	14.5

*Chi-square test, $p<0.05$.
**ANOVA, $p<0.05$.

Table 3. Regression Coefficients (95% CI) for the Effect of One Standard Deviation Difference in Serum High-Sensitivity CRP Levels on Markers of Hyperglycemia, Insulin Resistance and Anthropometric Measures

Marker	All Participants (n= 838)	
	Age and Gender Adjusted Model[a]	Multiple-Adjusted Model[b]
Fasting glucose (mg/dL)	1.200 (0.689; 1.710)*	0.445 (-0.056; 0.946)
2-h glucose (mg/dL)	0.732 (0.518; 0.945)*	0.289 (0.069; 0.508)*
Fasting insulin (mU/L)	0.352 (0.253; 0.452)*	0.072 (-0.035; 0.179)
2-h insulin (mU/L)	0.173 (0.090; 0.257)*	0.002 (-0.082; 0.085)
HOMA-IR†	0.582 (0.440; 0.725)*	0.175 (0.018; 0.332)*
BMI (kg/m^2)	0.104 (0.088; 0.121)*	0.066 (0.031; 0.101)*
Waist (cm)	0.040 (0.034; 0.047)*	0.035 (0.028; 0.042)*

All biochemical variables were log-transformed before analyses.
[a] Linear regression models adjusted for gender and age (years).
[b] Linear regression models adjusted for gender, age (years), generation (first/second generations), waist circumference (cm), smoking (never, past, current), hypertension (yes/no), dyslipidemia (yes/no), alcohol beverages (never, 0.2-54.0, > 54 g/day), practice of leisure time physical activity (yes/no).
†HOMA-R = [fasting glucose (mmol/L) x fasting insulin (mU/L)]/ 22.5.
*$p<0.05$.

been shown to be increased in the obese. Adipose tissue has been shown to express most of these proinflammatory mediators [2]. The origin of this proinflammatory state has been suggested to be related primarily to macronutrient intake, which may induce oxidative stress and inflammatory responses, as well as to genetic and other environmental factors that may induce the activation of inflammatory mechanisms [27]. Indeed, a recent article from the Diabetes Prevention Program reported the effect of an intensive lifestyle intervention or metformin on progression to diabetes in

Table 4. Odds Ratio (95% CI) for Each Glucose Tolerance Status According to Tertile of Serum High-Sensitivity CRP Levels

Glucose Tolerance Status		Tertiles of High-Sensitivity CRP Levels (mg/dl)			P-Value for Trend
		1	2	3	
Normal	No.	103	73	49	-
	Range	0.001–0.068	0.069–0.177	0.179–0.980	-
IFG	No.	80	66	48	-
	Range	0.001–0.068	0.069–0.177	0.180–0.936	-
	Age-gender adjusted	Reference	1.09 (0.69; 1.73)	1.24 (0.74; 2.07)	0.4090
	Model 1	Reference	0.93 (0.58; 1.51)	1.09 (0.64; 1.85)	0.8150
	Model 2	Reference	0.83 (0.51;1.37)	0.89 (0.51; 1.58)	0.6450
	Model 3	Reference	0.89 (0.53; 1.50)	0.80 (0.44; 1.46)	0.4620
IGT	No.	56	79	82	-
	Range	0.017–0.068	0.069–0.174	0.179-0.962	-
	Age-gender adjusted	Reference	1.88 (1.18; 3.00)*	2.76 (1.68; 4.53)*	0.0001
	Model 1	Reference	1.61 (0.98; 2.63)	2.61 (1.54; 4.44)*	0.0001
	Model 2	Reference	1.31 (0.79; 2.19)	1.83 (1.04; 3.22)*	0.0360
	Model 3	Reference	1.34 (0.80; 2.27)	1.87 (1.04; 3.37)*	0.0360
Type 2 diabetes	No.	48	71	83	-
	Range	0.010-0.068	0.069–0.177	0.179–0.965	-
	Age-gender adjusted	Reference	2.00 (1.22; 3.28)*	3.59 (2.15; 5.98)*	0.0001
	Model 1	Reference	1.81 (1.05; 3.13)*	2.87 (1.64; 5.03)*	0.0001
	Model 2	Reference	1.18 (0.65; 2.13)	1.22 (0.64; 2.32)	0.5520
	Model 3	Reference	0.94 (0.49; 1.82)	0.96 (0.46; 1.98)	0.9050

IFG = impaired fasting glucose; IGT = impaired glucose tolerance.
Model 1: multiple adjustment for gender, age (years), generation (first/second generations), smoking (never, past, current), hypertension (yes/no), dyslipidemia (yes/no), practice of leisure time physical activity (yes/no), alcohol beverages (never, 0.2–54.0, > 54 g/day), total energy intake, and tertiles of energy-adjusted dietary fiber.
Model 2: model 1 + waist circumference (cm).
Model 3: model 2 + HOMA-IR.
*p<0.05.

comparison to placebo in 3,234 adults with IGT. In the lifestyle group, weight loss rather than increased physical activity seemed to account for most of the changes in CRP concentrations (30% reduction in both genders) as compared with those in both placebo and metformin groups [28].

Our findings should be cautiously interpreted because there are some limitations to the present study. The principal constraint of our study is the cross-sectional design. Thus, we cannot establish a temporal relationship between exposure and outcomes to insure that elevations in CRP concentrations precede the onset of type 2 diabetes. Likewise, the temporal relation between abdominal weight gain and low-grade inflammation could not be assessed in this study. However, using a population-based design with detailed assessment of features related to glucose tolerance and insulin resistance status, the present study revealed highly significantly elevated CRP levels in individuals with IGT, independent of waist circumference and insulin resistance.

CONCLUSION

The present study suggests that low-grade inflammation increases the risk of IGT in Japanese-Brazilians but that some of the risk is confounded by abdominal obesity. Attenuation of this association after adjustment for factors related to insulin resistance reinforces the importance of the inflammation process in the disturbances of glucose metabolism.

Ethical Approval

The Institutional Ethics Committee of the Federal University of Sao Paulo approved the study protocol, and written informed consent was obtained from all participants.

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