AUTOIMMUNITY DOES NOT CONTRIBUTE TO THE HIGHLY PREVALENT GLUCOSE METABOLISM DISTURBANCES IN A JAPANESE BRAZILIAN POPULATION

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The Japanese Brazilian population has one of the highest prevalences of diabetes worldwide. Despite being non-obese according to standard definitions, their body fat distribution is typically central. We investigated whether a subset of these subjects had autoantibodies that would suggest a slowly progressive form of type 1 diabetes. A total of 721 Japanese Brazilians (386 men) in the 30- to 60-year age group underwent clinical examination and laboratory procedures, including a 75-g oral glucose tolerance test and determinations of serum autoantibodies. Antibodies to glutamic acid decarboxylase (GADab) were determined by radioimmunoassay and to thyroglobulin (TGab) and thyroperoxidase (TPOab) by flow-cytometry assays. Mean body mass index was 25.2 ± 3.8 kg/m^2, but waist circumference was elevated according to the Asian standards. Diabetes, impaired glucose tolerance, and impaired fasting glycemia were found in 31%, 22%, and 22%, respectively, and 53% of the subjects had metabolic syndrome. Glutamic acid decarboxylase (GADab) was positive in 4.72%, TGab in 9.6%, and TPOab in 10% of the whole sample. When participants were stratified according to the presence of thyroid antibodies, similar frequencies of GADab were found in positive and negative groups. The prevalence rates of glucose metabolism disturbances did not differ between GADab positive and negative groups. Our data did not support the view that autoimmune injury could contribute to the high prevalence of diabetes seen in Japanese Brazilians, and the presence of co-morbidities included in the spectrum of metabolic syndrome favors the classification as type 2 diabetes. (*Ethn Dis*. 2007;17:78–83)

Key Words: Diabetes, Glutamic Acid Decarboxylase Antibodies, Thyroid Antibodies, Metabolic Syndrome, Japanese Migrants

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INTRODUCTION

Japanese Brazilians have one of the highest prevalences of diabetes mellitus worldwide: 36.2% and a seven-year incidence of 30.9 per 1000 persons.[1] Environmental and lifestyle changes have been implicated in the increasing prevalence of diabetes among Japanese migrants. Weight gain is a direct consequence of changes in diet and physical activity, and obesity is one of the strongest risk factors for type 2 diabetes.[4] The World Health Organization (WHO) defines obesity as a body mass index (BMI) of 30 kg/m^2,[5] while the Japanese Society for the Study of Obesity defines it as ≥25 kg/m^2.[6] Japanese Brazilians are relatively non-obese when compared to the Brazilian general population,[7,8] but although overweight and obesity are more common in the Brazilian general population, the prevalence of diabetes is much higher in Japanese descendants living in Brazil under the same environmental conditions.[9] Such an intriguing situation has motivated a number of investigations.

Slight weight gain in Japanese people is associated with insulin resistance and diabetes.[10] Type 2 diabetic subjects are commonly non-obese and have reduced insulin response to glucose stimulation even during the preclinical phase.[11] The disease is markedly different from the classical type 2 diabetes seen in Caucasians, which is associated with obesity-induced insulin resistance.[12] Beta-cell deficiency occurs early in the course of the disease in Japanese subjects even in the prediabetic phase.[11] Proinsulin was predictive of diabetes in Japanese Americans[13]; this hormone could reflect primary lesions in beta cells during pathogenesis of type 2 diabetes. Reduced insulin secretion in response to oral glucose is found before the accumulation of intra-abdominal fat, which suggests that, in the natural history of the disease in Japanese subjects, beta-cell injury could occur before insulin resistance, which could be a consequence of hyperglycemia or obesity.[14] Genetic susceptibility could also play a role, since the general Brazilian population has less than half of the diabetes prevalence detected in Japanese Brazilians.[15]

Incidence of type 1 diabetes in Japanese persons is lower than in Caucasians. The subtype of slowly progressive type 1 diabetes – latent autoimmune diabetes (LADA)—is reported in both Japanese[16] and Caucasians[17] who tend to be classified as having type 2 diabetes. Latent autoimmune diabetes (LADA) could be diagnosed by circulating specific autoantibodies, such as the glutamic acid decarboxylase antibody (GADab), which is a sensitive and specific marker for autoimmune diabetes.[18] Type 1 diabetes may be associated with other autoimmune diseases. The Belgian Diabetes Registry found a 22% prevalence of thyroperoxidase antibodies in patients with type 1 diabetes.[19] Thyroid autoantibodies are common and may be present for years without progression to overt thyroid disease.[20] We hypothesized that autoimmune factors present among the Japanese Brazilian population could indicate an insulin secretion deficiency induced by immunologic injury that, in association with the genetic predisposition to metabolic syndrome, may account for the high prevalence of diabetes.

Table 1. Main clinical characteristics of 721 Japanese Brazilians (data expressed as mean ± standard deviation or number of subjects in parentheses)

N (men/women)	335 (46.5%)/386 (53.5%)
Age (years)	49.0 ± 8.0
Waist circumference (cm)	84.0 ± 10.0
Body mass index (kg/m^2)	25.2 ± 3.8
Mean blood pressure (mm Hg)	96.3 ± 16.5
HOMA-IR	2.7 ± 3.4
Glucose tolerance status (%)	
• Normal	26 (187)
• IFG	21 (154)
• IGT	22 (158)
• Diabetes	31 (222)
Metabolic syndrome (%)	53 (383)

HOMA-IR=homeostasis model assessment estimate of insulin resistance; IFG=impaired fasting glycemia; IGT=impaired glucose tolerance.

METHODS

A cross-sectional, population-based study on the prevalence of diabetes and associated diseases was conducted in Bauru, a developed city of São Paulo State, Brazil.[1] The entire Japanese Brazilian population older than 30 years of age was invited to participate. Details on the selection and recruitment of the sample were previously described.[7] Data from 1330 first-generation (born in Japan) and second-generation (born in Brazil) subjects were collected. The study was approved by the institutional ethics committee. After written informed consent was obtained, participants were interviewed at home with standardized questionnaires and scheduled for clinical and laboratory procedures after an overnight fast. A total of 187 healthy subjects with a normal glucose tolerance was used as controls. Characteristics of the subjects are described in Table 1. From 1330 Japanese Brazilians, 721 subjects (386 men, 335 women) within the age group 30–60 years were selected and screened for GADab, thyroperoxidase autoantibodies (TPOab), and thyroglobulin autoantibodies (TGab).

Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Waist circumference was measured at the midpoint between the lateral iliac crest and lowest rib. Blood pressure was measured three times after a 10-minute rest in the sitting position with an automatic device (Omron model HEM-712C, Omron Health Care, Inc, Bannockburn, Illinois, USA). Nondiabetic and self-reported diabetic subjects with fasting capillary glucose <11.1 mmol/L screened by glucose-oxidase strips were subjected to a two-hour 75-g oral glucose tolerance test. Glucose tolerance status was based on 1999 WHO criteria[21] or on the use of antidiabetic agents. In addition, blood samples were collected for lipid profile, insulin, and GAD and thyroid autoantibodies determinations. Using fasting glucose and insulin levels, the homeostasis model assessment estimate of insulin resistance (HOMA-IR) was determined.[22]

For the purpose of this study, metabolic syndrome definition was based on a modification of the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) criteria.[23] The NCEP requires at least three of the following components: fasting plasma glucose ≥110 mg/dL, waist circumference >102 cm or >88 cm (men or women), triglyceride ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL (men) or <50 mg/dL (women), and blood pressure ≥130/85 mm Hg. However, cutoff values for waist circumference were replaced with 90 cm for men and 80 cm for women to characterize central obesity in Japanese Brazilians, as proposed by a WHO committee for the Asia-Pacific region.[24]

Plasma glucose was determined by the glucose-oxidase method. Cholesterol contents of lipoprotein fractions and triglyceride were measured enzymatically. Glutamic acid decarboxylase antibody (GADab) was determined by a commercially available radioimmunoassay kit that used ^{125}I-labeled recombinant human GAD65 as a tracer reagent (SRS, Cambridge, United Kingdom). Sera were considered to be positive when the level exceeded the 95th percentile of the controls. The lowest and highest detection limits of the assay were .001 U/mL and 55.89 U/mL. SRS's assay based on ^{125}I-GAD shows excellent agreement with the 35S method in the different patient and control groups, and consequently it provides a convenient alternative.[25] SRS's GADab kit consistently gives 100% validity, 100% consistency, 100% sensitivity, and 100% specificity in GADab proficiency testing survey.[26] Thyroperoxidase (TPOab) and TGab were determined by a commercial flow-cytometry assay[27] using a Luminex 100 (Version 1.7. Austin, Texas, USA). The best cutoff value with better equivalence between diagnosis sensitivity and specificity for the presence of TPOab and TGab was based on a receiver operating characteristic curve and was set at 14 U/mL and 27 U/mL, respectively.

STATISTICS

Prevalence rates were estimated by point and 95% confidence interval (CI). Results are presented as means and standard deviations or medians with 25th and 75th percentiles. The Student unpaired *t* test was used to compare parameters between GADab-positive and GADab-negative subjects, and one-way analysis of variance was used for comparisons between the groups

Table 2. Median titers (25th and 75th percentiles) of thyroid autoantibodies according to glutamic acid decarboxylase antibody (GADab) positivity

	GADab positive (n=70)	GADab negative (n=636)	P value
TPOab (U/mL)	2.0 (1.2–5.9)	2.2 (1.1–4.0)	.3339
TGab (U/mL)	1.7 (.8–3.7)	1.7 (.9–4.0)	.7015

TPOab=thyroperoxidase antibody; TGab=thyroglobulin antibody.

according to glucose tolerance status. Antibody titers were compared by parametric and nonparametric tests; both types of tests provided the same statistical significance. Differences of frequencies for categorical variables were tested by the χ^2 test. Level of significance was set at $P<.05$. Statistical analysis was carried out by using the Stata 7.0 software package (version 7.0 for Windows; Stata Corporation, College Station, Texas, USA).

RESULTS

Serum samples were considered positive for concentrations>.80 U/mL. According to this criterion, 10 of 187 control subjects (5.4%) were GADab positive.

Prevalence of GADab According to Glucose Tolerance Status

Of 721 Japanese Brazilians screened, GADab was detected in 34 (4.7% [95% CI 3.3–6.5]) subjects. According to glucose tolerance status, GADab was detected in 10 (5.4% [95% CI 2.6–9.6]), 5 (3.3% [95% CI 1.1–7.4]), 6 (3.8% [95% CI 1.4–8.1]), and 13 (5.9% [95% CI 3.1–9.8]) of normal, impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), and diabetic groups, respectively. Such frequencies were not statistically different.

Glutamic acid decarboxylase antibody (GADab) mean values were similar when comparing the whole population (.47 ± 2.4 U/mL), normal (.46 ± 1.9 U/mL), IFG (.71 ± 4.6 U/mL), IGT (.43 ± 1.3 U/mL), and diabetic subjects (.33 ± .4 U/mL) (P=.510). Considering the extreme non-normal distribution, such data were shown as medians with 25th and 75th percentiles. Glutamic acid decarboxylase antibody (GADab) titers were similar for the whole sample (.24 U/mL [.13–.40 U/mL]), normal (.25 U/mL [.13–.39 U/mL]), IFG (.21 U/mL [.12–.4 U/mL]), IGT (.25 U/mL [.12–.39 U/mL]), and diabetic subjects (.25 U/mL [.13–.43 U/mL]).

Prevalence of Thyroid Autoantibodies

Thyroperoxidase (TPOab) was present in 9.9% (95% CI 7.8–12.4) and TGab in 9.6% (95% CI 7.5–12.0) of the whole population. The prevalence rates of both thyroid autoantibodies were higher in the female sex (TPOab 5.5% [95% CI 3.2–8.4] vs 13.9% [95% CI 10.5–17.8] and TGab 4.4% [95% CI 2.3–6.9] vs 14.4% [95% CI 10.9–18.3], P<.001). The median titers of thyroid autoantibodies were similar between GADab-positive and GADab-negative subjects (Table 2).

Prevalence and GADab Mean Titers According to Thyroid Autoantibodies

The prevalence of GADab did not differ between TPOab-positive (4.3% [95% CI .9–12.0]) and TPOab-negative (4.7% [95% CI 3.2–6.6]) groups (P=.871) and between TGab-positive (4.4% [95% CI .9–12.3]) and TGab-negative groups (4.6% [95% IC 3.2–6.6]) either (P=.916). No difference was detected between the median titers of GADab in groups stratified according to the presence of thyroid autoantibodies (Table 3).

Prevalence of Metabolic Syndrome and GADab Frequency

Of the 721 participants studied, 389 (54% [95% CI 50.2–57.6]) had metabolic syndrome. Japanese Brazilians with and without metabolic syndrome showed similar proportions of GADab (4.4 [95% CI 2.5–7.2] and 4.9% [95% CI 3.0–7.6], respectively, P=.741). No difference concerning mean values of age, BMI, waist circumference, blood pressure, HOMA-IR, or proportions of glucose metabolism disturbances and metabolic syndrome were detected when comparing GADab-positive and GADab-negative subjects. A significantly higher prevalence of metabolic syndrome was found in men than in

Table 3. Glutamic acid decarboxylase antibody (GADab) prevalence and median titers (25th and 75th percentiles) according to thyroid autoantibody positivity

	TPOab			Tgab		
	Positive n=70	Negative n=636	P value	Positive n=68	Negative n=639	P value
GADab prevalence (%)	4.3	4.7	.871	4.4	4.7	.916
GADab titer (U/mL)	.29 (.2–.4)	.24 (.1–.4)	.335	.28 (.2–.4)	.24 (.1–.4)	.349

TPOab=thyroperoxidase antibody; TGab=thyroglobulin antibody.

Table 4. Characteristics of glutamic acid decarboxylase antibody (GADab)-positive and GADab-negative subjects (data expressed as mean ± standard deviation; 95% confidence interval in parentheses)

	GADab positive	GADab negative	*P* value
N (men/women)	34 (22/12)	687 (313/374)	.029
Age (years)	50.3 ± 6.5	48.6 ± 7.8	0.221
Body mass index (kg/m^2)	26.2 ± 4.2	25.1 ± 3.8	.105
Waist (cm)	87.3 ± 9.7	83.3 ± 10.7	.033
Mean blood pressure (mm Hg)	99.1 ± 15.6	95.4 ±16.1	0.187
Plasma glucose (mg/dL)			
• Fasting	128.6 ± 43.6	122.3 ± 32.4	.283
• 2-hour	160.2 ± 82.6	155.4 ± 68	.703
HOMA-IR	2.4 ± 1.7	2.6 ± 3.5	0.642
HDL cholesterol	51.1 ± 8.1	49.8 ± 11.3	.516
Triglyceride	208.2 ± 100.5	187.8 ± 190.9	0.816
Glucose tolerance status (%)			
• IFG	14.7 (4.9–31.0)	21.7 (18.7–24.9)	.833
• IGT	17.6 (6.7–34.5)	22.1 (19.1–25.4)	.604
• Diabetes	38.2 (22.2–56.4)	30.4 (26.9–34.0)	.898
Metabolic syndrome (%)	55.9 (37.9–72.8)	52.9 (49.2–56.8)	.741

HOMA-IR=homeostasis model assessment estimate of insulin resistance; HDL=high-density lipoprotein; IFG=impaired fasting glycemia; IGT=impaired glucose tolerance.

women (60.0% [95% CI 54.5–65.3] vs 47.1% [95% CI 42.1–52.3], *P*=.001), as well as a higher prevalence of GADab in men than in women (6.6% [95% CI 4.2–9.8] vs 3.1% [95% CI 1.6–5.4], *P*=.029). Clinical and metabolic characteristics of subjects according to GADab positivity are given in Table 4.

DISCUSSION

Strong evidence has suggested that genetic susceptibility, together with unfavorable environmental conditions related to the Western lifestyle, may be responsible for higher prevalence of type 2 diabetes in Japanese descendants in the Americas when compared to people living in Japan.[7,28] As far as autoimmunity is concerned, reports on prevalence rates of GADab in adult diabetic populations in Japan are variable and do not confirm the role of autoimmunity in the high rates of disease in these populations. Glutamic acid decarboxylase antibody (GADab) positivity was found in 4.7% of adult Japanese Brazilians included in this population-based study. Our finding is similar to reports from Japan, since rates have ranged from 3% to 5% among subjects with classical manifestations of type 2 diabetes and from .6% to 2.2% among controls[16,29,30] and tended to be higher in those with slowly progressive diabetes (LADA). In the present study, disturbances of glucose tolerance in Japanese Brazilians were more closely related to other components of metabolic syndrome than with the slow progressive insulin-dependent diabetes mellitus proposed by Kobayashi et al.[16] Our finding of similar prevalence of GADab in subjects with diabetes when compared with the whole Japanese Brazilian population did not support a role of autoimmune dysfunction in the pathogenesis of diabetes.

In order to explore the suggested lack of association with autoimmunity, we examined the prevalence of thyroid autoantibodies which are commonly associated with autoimmune type 1 diabetes. Studies on the prevalence of thyroid antibodies in the general Brazilian population showed 4.8% of positivity for TPOab and 6.4% for TGab.[31] In healthy adults living in Sapporo, Japan, the prevalence of thyroid autoantibodies was of 6.4% in men and 13.8% in women.[19] In the present study, we did not find a greater prevalence of GADab or higher mean titers of GADab in TPOab- and TGab-positive subjects, which would be expected in type 1 diabetes.[32] Therefore, such findings are contrary to the hypothesis that an autoimmune component contributes to the high prevalence of diabetes in Japanese Brazilians.

A proportion of the Japanese Brazilian population that is genetically predisposed to insulin resistance is likely to experience weight gain, particularly of central distribution, and exhibit a variety of manifestations of metabolic syndrome in an unfavorable environment. Despite being non-obese, Japanese Brazilians commonly have increased waist circumferences[12] and high prevalence of the metabolic syndrome.[33] Even small amounts of weight gain, induced by lifestyle changes, should predispose to visceral fat accumulation and insulin resistance. The body of evidence in this population favors the hypothesis that Japanese migrants and their descendants in Brazil mainly develop type 2 diabetes.

In summary, Japanese Brazilians commonly have several abnormalities of the metabolic syndrome, the prevalence of glucose metabolism disturbances was not affected by presence of GADab, and GADab titers are similar among different glucose tolerance categories. On the basis of these data, we conclude that autoimmunity does not contribute to the high prevalence of diabetes seen in this population of Japanese ancestry living in the Western world.

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