Body Composition Is the Main Determinant for the Difference in Type 2 Diabetes Pathophysiology Between Japanese and Caucasians

Jonas B. Møller,[1] Maria Pedersen,[2] Haruhiko Tanaka,[3] Mitsuru Ohsugi,[3] Rune V. Overgaard,[1] Jan Lynge,[1] Katrine Almind,[1] Nina-Maria Vasconcelos,[1] Pernille Poulsen,[1] Charlotte Keller,[1] Kohjiro Ueki,[3] Steen H. Ingwersen,[1] Bente K. Pedersen,[2] and Takashi Kadowaki[3]

OBJECTIVE

This cross-sectional clinical study compared the pathophysiology of type 2 diabetes in Japanese and Caucasians and investigated the role of demographic, genetic, and lifestyle-related risk factors for insulin resistance and β-cell response.

RESEARCH DESIGN AND METHODS

A total of 120 Japanese and 150 Caucasians were enrolled to obtain comparable distributions of high/low BMI values across glucose tolerance states (normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes), which were assessed by oral glucose tolerance tests. BMI in the two cohorts was distributed around the two regional cutoff values for obesity.

RESULTS

Insulin sensitivity was higher in Japanese compared with Caucasians, as indicated by the homeostatic model assessment of insulin resistance and Matsuda indices, whereas β-cell response was higher in Caucasians, as measured by homeostatic model assessment of β-cell function, the insulinogenic indices, and insulin secretion ratios. Disposition indices were similar for Japanese and Caucasians at all glucose tolerance states, indicating similar β-cell response relative to the degree of insulin resistance. The main determinants for differences in metabolic indices were measures of body composition, such as BMI and distribution of adipose tissue. Differences in β-cell response between Japanese and Caucasians were not statistically significant following adjustment by differences in BMI.

CONCLUSIONS

Our study showed similar disposition indices in Japanese and Caucasians and that the major part of the differences in insulin sensitivity and β-cell response between Japanese and Caucasians can be explained by differences in body composition.

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Type 2 diabetes poses a global health problem approaching epidemic proportions. The number of patients with diabetes, estimated at 285 million in 2010, is expected to rise to an alarming level of 439 million by 2030 (1), mainly as a result of lifestyle shifts as currently seen in many Asian countries (2). Lifestyle factors and ethnicity are known determinants for development of type 2 diabetes (3). The importance of

[1]Novo Nordisk A/S, Bagsvaerd, Denmark
[2]Center of Inflammation and Metabolism, Rigshospitalet, Copenhagen, Denmark
[3]Department of Metabolic Diseases, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Corresponding author: Steen H. Ingwersen, si@novonordisk.com.

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lifestyle factors has been shown by a higher incidence of type 2 diabetes for Japanese Americans compared with native Japanese, mainly caused by higher fat intake and less physical activity following adaptation to a Western lifestyle (4).

Type 2 diabetes is characterized by hepatic and peripheral (including skeletal muscle and adipose tissue) insulin resistance and β-cell failure (5). It is thought to be triggered by insulin resistance, which is compensated initially by increased β-cell response, leading eventually to type 2 diabetes due to exhaustion of the pancreas (5–7). According to current understanding, the pathophysiology of type 2 diabetes is different in Japanese compared with Caucasians in the sense that Japanese are unable to compensate insulin resistance with increased insulin secretion to the same extent as Caucasians. Prediabetes and early stage diabetes in Japanese are characterized by reduced β-cell function combined with lower degree of insulin resistance compared with Caucasians (8–10). In a prospective, cross-sectional study of individuals with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT), it was demonstrated that Japanese in Japan were more insulin sensitive than Mexican Americans in the U.S. and Arabs in Israel (11). The three populations also differed with regards to β-cell response, whereas the disposition index—a measure of insulin secretion relative to insulin resistance—was similar across ethnicities for NGT and IGT participants. These studies suggest that profound differences in type 2 diabetes pathophysiology exist between different populations. However, few attempts have been made to establish the underlying demographic or lifestyle-related factors such as body composition, physical fitness, and physical activity leading to these differences.

The current study aimed at comparing Japanese and Caucasians at various glucose tolerance states, with respect to *1*) insulin sensitivity and β-cell response and *2*) the role of demographic, genetic, and lifestyle-related factors as underlying predictors for possible ethnic differences in insulin sensitivity and β-cell response. To our knowledge, this is the first prospective, cross-sectional study in well-characterized Japanese and Caucasians living in their respective country of origin and spanning the range of glucose tolerance from NGT to IGT and type 2 diabetes. In order to account for the influence of body composition on glucose homeostasis, comparable proportions of individuals with high and low BMI, respectively, were included in each of the Japanese and Caucasian glucose tolerance state subgroups.

RESEARCH DESIGN AND METHODS

Study Design

The study investigated 150 Caucasians (of Northern European background for at least three generations) enrolled at Copenhagen University Hospital, Denmark, and 120 Japanese (of Japanese background for at least three generations) enrolled at Tokyo University Hospital, Japan. The aim was to recruit three glucose tolerance groups (NGT, IGT, and type 2 diabetes) with comparable age, sex, and BMI classification (high/low). Potential participants (males and females aged 40–65 years) were screened to exclude individuals with metabolic conditions other than type 2 diabetes such as monogenic forms of diabetes and latent autoimmune diabetes in adults. Other key exclusion criteria were insulin treatment, recent/ongoing infection, history of malignant disease, use of thiazolidinedione-based medications within 3 months, or unstable body weight (±10%) for the past year. Participation also required normal results from the physical examination; electrocardiogram; blood tests for renal function (creatinine), hepatic function (alanine aminotransferase), and thyroid function (thyroid-stimulating hormone); hemoglobin; white blood cell counts; and electrolytes and urinalysis. Participants were classified as having either NGT, IGT, or type 2 diabetes (12) on the basis of blood glucose levels while fasting and at 2 h during an oral glucose tolerance test (OGTT). Participants in both countries were assigned into similarly sized groups of low and high BMI to obtain comparable distributions of BMI across glucose tolerance states. Low BMI was defined for Japanese as <25 kg/m^2 and for Caucasians as <30 kg/m^2, in accordance with regional obesity definitions (13,14). Consequently, the BMI distributions were balanced around the two regional cutoffs of 25 and 30 kg/m^2, respectively.

The study protocol was approved by the Regional Committee on Biomedical Research Ethics in Denmark (journal number H-C-2008-101) and by the Research Ethics Committee, Graduate School of Medicine, University of Tokyo, Japan. Informed consent was obtained from all participants, and the data handling was approved by the Danish Data Protection Agency.

Procedures

At visit 1, participants reported to the clinic in the morning after fasting overnight. They were evaluated according to the inclusion and exclusion criteria, and demographic characteristics were assessed. Concomitant medication, physical condition (including body measurements), and vital signs were recorded, and blood samples were collected for hematological and biochemical assessment. For the Japanese cohort, which was smaller than the Danish cohort, an indicatory OGTT was conducted to assist recruitment into glucose tolerance states.

Assessment of Body Composition, Physical Fitness, and Activity Habits

Body composition was estimated by dual-energy X-ray absorptiometry. Regions of interest were determined from scans using software provided by the manufacturer (Lunar prodigy, GE Medical System, WI). Fat and fat-free tissue mass in whole body and fat mass in trunk, legs, arms, and android and gynoid regions were measured as described (15). Android fat is localized in the abdominal region and gynoid fat around the hip. A spine phantom was scanned daily for quality control. All scans were reviewed and analyzed by the same person at each site.

Physical fitness was measured by the single-stage model to estimate VO_{2max}. The VO_{2max} test was performed on a cycle ergometer and calculated according to Aastrand (16). This

submaximal test is feasible to use in individuals not used to intense physical activity (17). Physical activity habits were investigated by means of the International Physical Activity Questionnaire (18).

Assessment of Insulin Sensitivity and β-Cell Function

Female participants were scheduled to visit 2 within the 14th day ±4 days of their menstruation cycle. At visit 2, all participants underwent an OGTT with an oral bolus corresponding to 75 g glucose. Plasma samples for measurement of glucose, insulin, and C-peptide concentrations were collected at times –30, 0, 10, 20, 30, 60, 90, 120, 150, 180, 240, and 300 min relative to the time of glucose ingestion. All samples were stored frozen before assay at a central laboratory in Denmark (Unilabs, Copenhagen, Denmark). The homeostatic model assessment of insulin resistance (HOMA-IR) index for insulin resistance while fasting was calculated using the approximated equation of Matthews et al. (19), and the Matsuda index to assess insulin action was obtained using fasting values as well as mean levels of glucose and insulin from time 0 to 120 min following glucose challenge (20). β-Cell response at fasting condition was evaluated by homeostatic model assessment of β-cell function (HOMA-B), which is based on fasting glucose and insulin concentrations and calculated using the approximated equation of Matthews et al. (19). β-Cell response following glucose challenge was evaluated using insulin as well as C-peptide-based secretion indices. The insulinogenic index was calculated from insulin and glucose concentrations at fasting and 30 min after glucose challenge (21), and the insulin secretion ratio was obtained from the ratio of incremental area under the curve values for insulin and glucose calculated from 0 to 120 min following glucose intake (22). The prehepatic insulinogenic index and insulin secretion ratio were based on insulin secretion rates obtained by deconvolution of C-peptide data (23) and glucose concentrations. The prehepatic insulinogenic index was calculated as the increment of insulin secretion rate from 0 to 30 min divided by the increment in glucose concentration during the same time interval. The prehepatic insulin secretion ratio was calculated as the incremental area under the insulin secretion rate from time 0 to 120 min divided by the incremental area under the glucose concentration profile during the same time interval.

β-Cell response relative to the degree of insulin resistance was evaluated by the disposition index, which was calculated as the product of the insulinogenic index and the Matsuda index (24), as well as the product of the insulin secretion ratio and the Matsuda index (22).

Single Nucleotide Polymorphisms

At visit 2, blood was collected onto Whatman FTA cards, from which DNA was extracted and analyzed for single nucleotide polymorphisms (SNPs) in genes with established association with type 2 diabetes susceptibility at the time of analysis. Genotyping was performed by Cogenics Inc. (Morrisville, NC).

A genetic secretion risk score for β-cell response was calculated using information on risk alleles for SNPs with known association with insulin secretion (*CDKN2A rs10811661*, *MTNR1B rs10830963*, *CDKAL1 rs10946398*, *SLC30A8 rs13266634*, *DGKB rs2191349*, *KCNQ1.a rs2237895*, *IGF2BP2 rs4402960*, *KCNJ11 rs5219*, *C2CDA4A/B rs7172432*, and *TCF7L2 rs7903146*). To calculate this score, we combined the information of the SNPs using an allele count model (25), where homozygotes for risk alleles were assigned a value of 2 and heterozygotes a value of 1 to obtain the total sum of risks over all SNPs related to β-cell response assuming an equal and additive effect of each allele. A single SNP with a known association with insulin resistance (*PPARG rs1801282*) was analyzed as predictive factor for the Matsuda index.

Statistical Analysis

Covariate relations for the Matsuda and insulinogenic indices were evaluated using log-linear ANCOVA models. The dependent variable (Y) was either the Matsuda index or the insulinogenic index, whereas glucose tolerance state (type), ethnicity, the interaction between the two, and the given covariate were included as independent variables ($\log Y \sim$ ethnicity + type + ethnicity:type + covariate). *P* values presented in Table 2 represent the significance of each covariate (included one at a time) using the above ANCOVA model. The percentage of variance explained by each covariate was obtained using residuals from the model, with and without inclusion of each covariate (Table 2). Furthermore, the signs of the log-linear relations between each of the significant covariates and the Matsuda index and the insulinogenic index, respectively, were included in Table 2 to show interrelationships between insulin sensitivity and β-cell response.

P values for ethnicity (Figs. 1–2 and Supplementary Fig. 2) and interaction between ethnicity and glucose tolerance state were obtained from a similar model as defined above, with and without BMI included in the model as covariate.

RESULTS

Baseline characteristics of the study participants (Table 1) showed similar demographic distributions for the two ethnic cohorts, except for height, weight, and BMI, which were lower in Japanese than in Caucasians. As expected, the difference in mean BMI values (25.0 kg/m^2 in Japanese and 30.8 kg/m^2 in Caucasians) reflects the different inclusion criteria, which is in line with the cutoff values for obesity in the two regions. Fasting plasma glucose levels were similar across ethnicities, whereas serum insulin, C-peptide, and HbA_{1c} baseline levels were higher in Caucasians than in Japanese. VO_{2max} (mL/min/kg) was lower in Caucasians than in Japanese.

OGTT mean concentration profiles of plasma glucose, serum insulin, and serum C-peptide are shown in Supplementary Fig. 1. Glucose levels were similar for the two cohorts with regards to magnitudes and profile shapes. In contrast, serum insulin and C-peptide responses appeared lower in Japanese compared with Caucasians at all glucose tolerance states.

The insulin resistance (expressed by HOMA-IR) was generally more pronounced in Caucasians than in

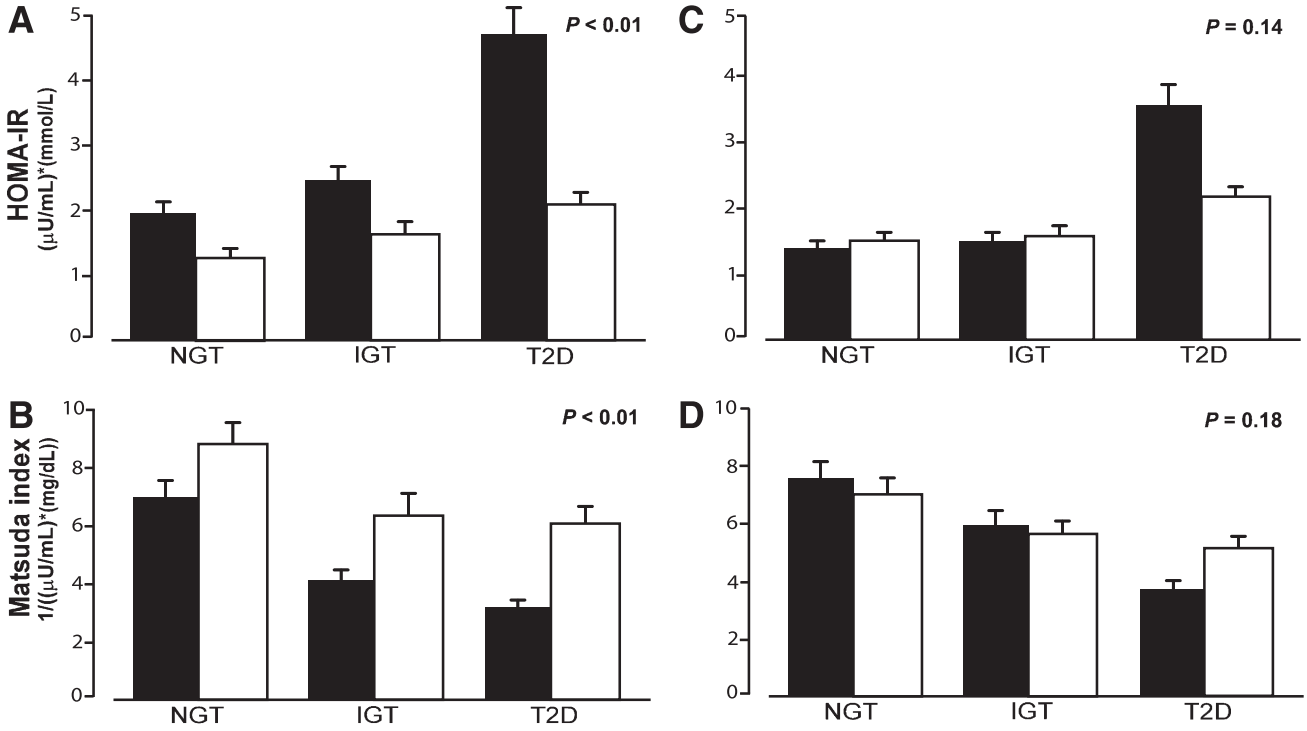

Figure 1—Summary of insulin sensitivity indices by ethnicity and glucose tolerance state with (*right panels*) and without (*left panels*) adjustment for BMI. Data are mean ± SEM for (*A*) HOMA-IR and (*B*) the Matsuda index. The corresponding BMI-adjusted values (*C* and *D*). Data and significance values for ethnic difference were obtained from ANCOVA models. T2D, type 2 diabetes; black bars, Caucasians; white bars, Japanese.

Japanese, and insulin sensitivity as measured by the Matsuda index was higher in Japanese than in Caucasians across glucose tolerance states (Fig. 1*A* and *B*).

The insulinogenic index and the prehepatic insulinogenic index declined progressively from NGT to type 2 diabetes in both cohorts (Fig. 2*A* and *B*). Differences were evident for the insulinogenic index, showing significantly higher values in Caucasians compared with Japanese ($P < 0.01$). In contrast, no difference was seen for the prehepatic insulinogenic index based on C-peptide values ($P = 0.30$). In Japanese, HOMA-B was found to be lower than in Caucasians (Supplementary Fig. 2*A*). HOMA-B appeared similar in NGT and IGT and decreased from IGT to type 2 diabetes in Japanese as well as in Caucasians. For the insulin secretion ratio and the prehepatic insulin secretion ratio, similar patterns were seen across glucose tolerance groups in Caucasians and Japanese, and both ratios were higher in Caucasian than in Japanese individuals (Supplementary Fig. 2*B* and *C*).

To obtain a measure of the β-cell response relative to the degree of insulin resistance, the disposition index was calculated for the NGT, IGT, and type 2 diabetes groups, using the unadjusted values of the insulinogenic index and the insulin secretion ratio, respectively, for β-cell response and the Matsuda index for insulin sensitivity. As shown in Fig. 2*E* and Supplementary Fig. 2*G*, both disposition indices declined from NGT to IGT and further to type 2 diabetes in both cohorts. No statistically significant differences between Japanese and Caucasians were found for disposition indices at any of the glucose tolerance states, suggesting that insulin resistance was compensated by insulin secretion to the same extent in Japanese and Caucasians.

We investigated the interindividual variation of the Matsuda and insulinogenic indices using ANCOVA models to establish relations between demographic, genetic, and lifestyle-related covariates and insulin sensitivity and β-cell response, respectively (Table 2). For the Matsuda index, waist circumference, android fat, hip circumference, BMI, weight, and trunk fat explained most of the variance (>20% each). Triglycerides, physical fitness (VO_{2max} per kilogram), waist-to-hip ratio, whole-body fat, and HDL were of medium importance (between 10 and 20% each), whereas the total physical activity score as obtained from International Physical Activity Questionnaire was of minor importance (<0.1%). *PPARG*, a genetic marker for insulin resistance, explained 2.7% of the variance. Additionally, factors such as gynoid fat, lower-limb fat, LDL, cholesterol, and age were also of minor importance (<2% each).

For the insulinogenic index (Table 2) the android fat, waist circumference, trunk fat, BMI, and hip circumference were the single factors that explained most of the variance (>10% each). Body weight, whole-body fat, and triglycerides were of medium importance (5–10% each). VO_{2max} explained 4.9% of the variance, whereas total physical activity was of minor importance (1.6%). The genetic risk score for insulin secretion was significant but explained only 2.8% of the variance of the insulinogenic index.

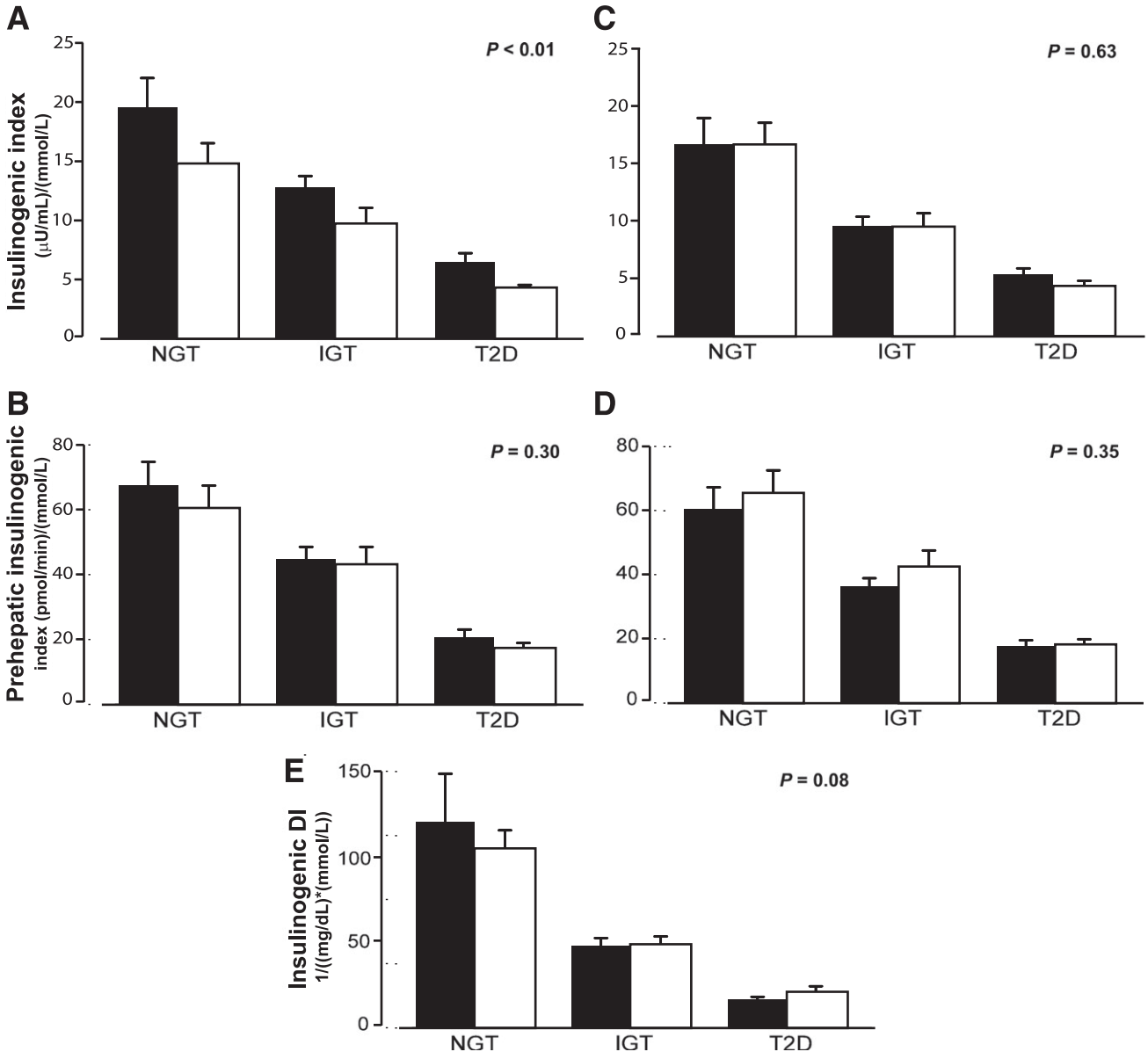

Figure 2—Summary of β-cell response indices by ethnicity and glucose tolerance state. β-Cell response indices are shown with (*right panels*) and without (*left panels*) adjustment for BMI. Data are mean ± SEM for (*A*) the insulinogenic index and (*B*) the prehepatic insulinogenic index based on C-peptide. The corresponding BMI-adjusted values (*C* and *D*). The disposition index obtained from the Matsuda index and the insulinogenic index (*E*). Data and significance values for ethnic difference were obtained from ANCOVA models. T2D, type 2 diabetes; DI, disposition index; black bars, Caucasians; white bars, Japanese.

Waist-to-hip ratio, gynoid fat, HDL, lower-limb fat, cholesterol, and age were all of minor importance (<5% each).

As seen in Table 2, the slopes of the covariate relationships, which were estimated for the significant covariates, were of opposite signs for the Matsuda index and the insulinogenic index. This finding supports the hypothesis that the observed ethnic differences in β-cell response are driven by differences in insulin sensitivity.

Among the covariate factors investigated above, we focused specifically on BMI, a well-established marker of body composition, which was also a design parameter for the study. BMI was among the most important covariates for insulin sensitivity and β-cell response (Table 2). Similar log-linear relationships between measures of insulin sensitivity or β-cell response and BMI were found for the two ethnic cohorts (details not shown). This finding, in combination with the inherent difference in BMI in the two cohorts (related to the study design; see Table 1), led us to estimate BMI-adjusted estimates of insulin sensitivity and β-cell response. Specifically, individual values of insulin sensitivity and β-cell response indices were adjusted to the overall median value for the entire study population. As shown in Fig. 1*C* and *D*, differences in the two indices of insulin sensitivity (HOMA-IR and Matsuda index) were reduced to a considerable extent following BMI

Table 1—Baseline characteristics of participants

	Caucasians				Japanese			
	NGT	IGT	T2D	Total	NGT	IGT	T2D	Total
Number of subjects	63	39	48	150	46	26	48	120
Low BMI[a] (%)	32 (51)	14 (36)	24 (50)	72 (48)	25 (54)	12 (46)	27 (56)	64 (53)
Age (years)	53 (7)	54 (8)	57 (7)	55 (7)	49 (7)	54 (8)	57 (7)	54 (8)
Sex (male) (%)	29 (46)	15 (38)	29 (60)	73 (49)	21 (46)	12 (46)	33 (69)	66 (55)
Height (m)	1.74 (0.11)	1.71 (0.10)	1.76 (0.10)	1.74 (0.10)	1.63 (0.10)	1.62 (0.10)	1.64 (0.08)	1.63 (0.09)***
Weight (kg)	90.3 (21)	97.7 (22)	94.0 (21)	93.4 (21)	64.6 (13)	69.6 (18)	68.0 (13)	67.1 (14)***
BMI (kg/m^2)	29.8 (5.9)	33.0 (6.3)	30.4 (5.7)	30.8 (6.1)	24.0 (3.2)	26.3 (5.0)	25.3 (4.4)	25.0 (4.2)***
Waist-to-hip ratio	0.91 (0.09)	0.94 (0.08)	0.97 (0.08)	0.94 (0.09)	0.93 (0.05)	0.94 (0.05)	0.95 (0.05)	0.94 (0.05)
FPG (mmol/L)	5.5 (0.5)	5.9 (0.4)	8.3 (2.0)	6.5 (1.7)	5.5 (0.5)	6.0 (0.6)	7.7 (1.3)	6.5 (1.3)
FSI (pmol/L)	46 (36)	56 (34)	77 (47)	58 (41)	30 (19)	36 (24)	36 (23)	34 (22)***
FS C-peptide (nmol/L)	0.74 (0.30)	0.89 (0.27)	1.13 (0.42)	0.90 (0.37)	0.57 (0.22)	0.66 (0.32)	0.70 (0.20)	0.64 (0.25)***
HbA_{1c} (%)	5.5 (0.3)	5.7 (0.4)	6.6 (0.9)	5.9 (0.8)	5.2 (0.3)	5.5 (0.3)	6.2 (0.7)	5.7 (0.7)*
HbA_{1c} (mmol/mol)	36.6 (3.5)	38.8 (3.8)	48.2 (10)	40.9 (8.2)	33.5 (2.9)	36.5 (3.2)	44.3 (7.1)	38.5 (7.1)*
VO_{2max} (mL/min/kg)	28.0 (9.9)	24.9 (6.1)	24.7 (6.4)	26.1 (8.1)	31.7 (7.2)	29.8 (7.4)	27.6 (7.8)	29.7 (7.7)***

T2D, type 2 diabetes; FPG, fasting plasma glucose; FSI, fasting serum insulin; FS, fasting serum. Data are presented as number of participants (%) or mean (SD). To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for insulin to milliunits per liter, divide by 6. *P* values for differences between the Japanese and Caucasian cohorts were obtained from two-sided unpaired *t* tests. [a]Cutoffs for the low-BMI group were $<$25 and $<$30 kg/m^2 for Japanese and Caucasians, respectively. ***$P < 0.001$. *$P < 0.05$.

adjustment and were no longer significant. Significant interactions between ethnicity and glucose tolerance state were still present after BMI adjustment of HOMA-IR ($P < 0.01$) as well as the Matsuda index ($P < 0.05$), attributed to differences between the two groups of type 2 diabetes patients. For all five indices of β-cell response (insulinogenic index, prehepatic insulinogenic index, insulin secretion ratio, prehepatic insulin secretion ratio, and HOMA-B), differences between Caucasians and Japanese were no longer present after accounting for BMI (Fig. 2*C* and *D* and Supplementary Fig. 2*D*–*F*).

CONCLUSIONS

This study was conducted to investigate *1*) whether Caucasians and Japanese have similar β-cell response and insulin sensitivity across glucose tolerance states and *2*) whether differences found in metabolic indices can be explained by demographic, genetic, or lifestyle-related risk factors.

In our study, glucose profiles from OGTTs were similar in Japanese and Caucasians, whereas insulin and C-peptide responses were lower in Japanese participants compared with Caucasians. In line with these observations, measures of β-cell response were generally lower in Japanese, who simultaneously had higher insulin sensitivity. Moreover, β-cell response relative to the degree of insulin resistance as measured by disposition indices was virtually identical in the two populations.

Assessments of insulin sensitivity and β-cell function at various glucose tolerance states have previously been performed in the Botnia study (26), which showed an apparent increase in the mean insulin response following an OGTT from NGT to IGT and a decrease from IGT to type 2 diabetes. However, when the insulin response was evaluated relative to the glucose concentration, there was a significant decline both from NGT to IGT and from IGT to type 2 diabetes. In addition, the HOMA-IR increased from NGT to type 2 diabetes, reflecting the natural history of type 2 diabetes. Our study found similar changes in the mean insulin response in Japanese, namely, an apparent increase from NGT to IGT and a decrease from IGT to type 2 diabetes. A gradual decline from NGT to IGT and from IGT to type 2 diabetes in Japanese insulin response was also observed after accounting for the glucose concentration.

We identified BMI, waist circumference, android fat, and body weight as major determinants of insulin sensitivity and β-cell response. This finding is in accordance with previous findings demonstrating abdominal obesity as determinant of insulin resistance (27). Physical condition as estimated from VO_{2max} test was also a significant determinant, but of less importance than the above-mentioned factors. The limited quantitative importance of the known genetic risk factors is in accordance with previous findings (28), and this may change with the identification of future risk factors.

Several of the covariates investigated in this study are mutually correlated, which limits the evaluation of possible causative relationships. Importantly, BMI and android fat were highly correlated ($r = 0.79$), and we selected BMI, which was a design parameter of the study, for a more comprehensive investigation of differences between the Caucasian and Japanese cohorts. In fact, the observed differences in insulin sensitivity and β-cell response between the two ethnic cohorts could be explained by BMI. After accounting for BMI, the ethnic differences were no longer statistically significant for any of the studied metabolic indices.

Our study confirmed the previous findings that Japanese are characterized by a lower degree of insulin resistance

Table 2—Contribution of covariate factors for Matsuda and insulinogenic indices

	Matsuda index			Insulinogenic index		
Covariate (unit)	*P* value	Percentage of variance explained[a]	Sign of covariate relationship[b]	*P* value	Percentage of variance explained[a]	Sign of covariate relationship[b]
Waist (cm)	<0.001	39.9	−	<0.001	12.3	+
Android fat (%)	<0.001	39.8	−	<0.001	15.8	+
Hip (cm)	<0.001	30.6	−	<0.001	10.5	+
BMI (kg/m^2)	<0.001	30.5	−	<0.001	11.7	+
Weight (kg)	<0.001	29.9	−	<0.001	9.4	+
Trunk fat (%)	<0.001	29.3	−	<0.001	12.2	+
Triglycerides (mmol/L)	<0.001	17.3	−	<0.001	5.9	+
VO_{2max} per kg (mL/min/kg)	<0.001	17.3	+	0.001	4.9	−
Waist-to-hip ratio	<0.001	16.6	−	0.001	3.7	+
Whole-body fat (%)	<0.001	15.3	−	<0.001	7.7	+
HDL (mmol/L)	<0.001	13.5	+	0.010	2.1	−
Genetic secretion score	NA	NA	NA	0.003	2.8	−
Genetic insulin sensitivity score	0.195	2.7	NA	NA	NA	NA
Gynoid fat (%)	0.025	1.8	NA	0.006	2.5	+
Lower-limb fat (%)	0.073	1.2	NA	0.019	1.7	NA
LDL (mmol/L)	0.134	0.9	NA	0.116	1.0	NA
Cholesterol (mmol/L)	0.446	0.2	NA	0.294	0.4	NA
Age (years)	0.308	0.2	NA	0.238	0.4	NA
Total activity score (MET)	0.850	<0.1	NA	0.040	1.6	NA

P values were obtained from log-linear models having Matsuda index and the insulinogenic indices, respectively, as dependent variable and each covariate, glucose tolerance state, and ethnicity as independent variables. MET, metabolic equivalent of task; NA, not applicable. [a]Explained variance was calculated using the variance of residuals from log-linear models with and without each covariate included as independent factor. [b]+ or − indicate positive or negative slopes for covariate relationship. Slopes for nonsignificant relationships ($P > 0.01$) were not reported.

and a concomitantly reduced β-cell response compared with Caucasians, regardless of glucose tolerance state (8), and showed that these differences were associated with differences in body composition, expressed as BMI. The observed relationship between insulin sensitivity and BMI is well established in both Japanese and Caucasians (29–31), confirming that obesity is a risk factor for type 2 diabetes (32,33). The strong correlation between BMI and β-cell response was most likely driven by increased insulin resistance with increasing BMI, reflecting the compensatory nature of the β-cell in response to insulin resistance. Our finding of similar disposition indices in Japanese and Caucasians suggests equal ability to compensate an insulin resistance with increased β-cell response.

In contrast to previous studies investigating pathophysiological differences in type 2 diabetes between Caucasians and Japanese, this study assigned participants into two groups of low and high BMI, respectively, for each of the glucose tolerance states: NGT, IGT, and type 2 diabetes. This secured similar BMI distributions around the regional cutoff for obesity in each of the glucose tolerance states. This enabled us to study cohorts representative of the general body composition in the two countries and to assess the importance of body composition for insulin sensitivity and secretion. An alternative approach could be to study Japanese and Caucasian cohorts with identical BMI, but this design is likely to be of limited value with regards to inferences for the general populations.

One question left to be addressed is why Japanese seem to develop type 2 diabetes at a lower BMI than do Caucasians (34). Differences in diabetes-related fat depots, such as visceral and subcutaneous fat, which were not measured in our study, may be responsible for this. Future longitudinal studies including such assessments would provide further insight into ethnic differences in progression of type 2 diabetes.

In conclusion, our study showed similar disposition indices in Japanese and Caucasians. We also confirmed the existence of differences in insulin sensitivity and β-cell response between Japanese and Caucasians and showed for the first time that a major part of these differences can be explained by differences in body composition such as BMI. On the basis of these results, we propose a similar pathophysiology of type 2 diabetes in Caucasians and Japanese with respect to insulin sensitivity and β-cell function.

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