Insulin Sensitivity, Glucose Effectiveness, and Body Fat Distribution Pattern in Nondiabetic Offspring of Patients With NIDDM

Kwame Osei, MD
Daryl A. Cottrell, MD
Martha M. Orabella, RD

Objective: To determine the relationship of insulin sensitivity (S_I), glucose effectiveness (glucose-dependent glucose transport [S_G]), and body fat distribution patterns in glucose-tolerant offspring of patients with non-insulin-dependent diabetes mellitus (NIDDM). Research Design and Methods: Ten glucose-tolerant offspring of patients with NIDDM and 10 age-, sex-, and weight-matched healthy control subjects without family history of diabetes were studied with the minimal model method of Bergman et al. Body fat composition and distribution pattern were assessed by the bioelectrical impedance analyzer and waist-hip circumference ratios (WHR), respectively, in each subject. Results: Mean fasting serum glucose (4.39 ± 0.17 vs. 3.94 ± 0.17 mM) and postglucose peak (18.50 ± 1.50 vs. 13.20 ± 1.06 mM) levels were significantly greater ($P < 0.05$) in the offspring than in the control subjects. Mean fasting serum insulin levels were slightly greater but not significantly different in the offspring versus control subjects (64 ± 14 vs. 29 ± 7 pM). After intravenous stimulation with glucose and tolbutamide, the mean serum insulin rose to significantly greater ($P < 0.05$) levels at $t = 5$ and 25 min in the offspring compared with the control subjects. Mean S_I was significantly reduced by 45% in the offspring compared with the control subjects (4.77 ± 0.67 vs. 8.37 ± 1.24 × 10^{-4} $min^{-1} \cdot mU^{-1} \cdot L^{-1}$). However, S_G was not different in the offspring versus control subjects (1.92 ± 0.12 vs. 2.10 ± 0.17 × 10^{-2} min^{-1}). S_I correlated significantly and inversely with the percentage of body fat mass ($r = -0.580$, $P < 0.05$) but not with the WHR ($r = -0.019$) in the offspring. We found a negative association between S_I and basal serum insulin ($r = -0.798$, $P < 0.01$) but not with the poststimulation incremental insulin responses in the offspring. Family history of diabetes independently accounted for at least 27% of variance in the S_I in our subjects. Conclusions: Our study confirmed that insulin insensitivity but not a reduced glucose effectiveness exists in young glucose-tolerant offspring of patients with NIDDM. The reduced S_I appears to be causally related to the total body fat content and may be a familial and/or genetic trait in the offspring. *Diabetes Care* 14:890–96, 1991

Non-insulin-dependent diabetes mellitus (NIDDM) is a genetic and familial disease (1–3). Recent studies in nondiabetic first-degree relatives and offspring of patients with NIDDM have demonstrated that severe insulin resistance appears to antecede or precede the development of impaired glucose tolerance (IGT) and clinical diabetes (4–10). The first-degree relatives are often characterized by basal and/or postglucose hyperinsulinemia in some previous studies (9,11) but not in others (5,12). Thus, the hyperinsulinemia could be viewed as a compensatory mechanism for the insulin-resistant state. However, despite the reduction in insulin-mediated glucose disposal equivalent to that of patients with NIDDM and IGT, it is ironic that most young relatives often maintain normal glucose tolerance with relatively normal insulin concentrations. Thus, these previous studies cannot entirely explain the normal glucose tolerance in the offspring.

Because total glucose disposal in humans consists of insulin- and non–insulin-mediated glucose disposal, it could be hypothesized that in the face of severely di-

From the Department of Internal Medicine, Division of Endocrinology and Metabolism, The Ohio State University Hospitals, Columbus, Ohio.
Address correspondence and reprint requests to Kwame Osei, MD, 485 McCampbell Hall, 1581 Dodd Drive, Columbus, OH 43210-1296.
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minished insulin-mediated glucose disposal, normal glucose tolerance could only be achieved by at least a normal glucose-dependent glucose transport (S_G) and/or augmented β-cell insulin secretion. Bergman (13) demonstrated that reduction in S_G is a necessary prerequisite for the development of hyperglycemia in NIDDM patients. Furthermore, Finegood et al. (14) have shown that both insulin sensitivity (S_I) and S_G were markedly reduced in newly diagnosed patients with insulin-dependent diabetes mellitus (IDDM). Although S_I was normalized during non–insulin-requiring clinical remission, S_G remained decreased in their IDDM subjects. Thus, whether the reduction in S_G precedes deterioration in glucose levels or is a concomitant feature of poor glucose control remains uncertain from these studies. Indeed, several recent studies have indicated that hyperglycemia impairs β-cell function and insulin sensitivity in experimental animals. Therefore, a study in genetically predisposed but nondiabetic offspring of NIDDM patients to simultaneously evaluate S_G, S_I, and β-cell function without antecedent hyperglycemia could provide important data on the early etiopathogenesis of NIDDM. In this respect, Bergman (13) has suggested that at least 80% reduction in both S_I and S_G is necessary for the development of NIDDM. Because there is overwhelming evidence that has indicated that obesity and upper-body fat distribution patterns are associated with alterations in glucose metabolism, insulin resistance, and hyperinsulinemia, it is imperative to examine the relationships of various anthropometric parameters to these metabolic variables in the studies evaluating glucose-tolerant offspring of patients with NIDDM.

Therefore, we used the minimal model technique of Bergman (13) to quantitate the S_I, S_G, and disposition index (a measure of S_I and β-cell parameter) in 10 glucose-tolerant offspring of patients with NIDDM and 10 age-, sex-, and weight-matched healthy control subjects with no family history of diabetes. The goals of the study were to *1*) determine whether alterations in these parameters occurred in the nondiabetic offspring of parents with NIDDM and *2*) examine the impact of body fat distribution patterns and family history of diabetes on these metabolic variables.

RESEARCH DESIGN AND METHODS

The study population consisted of 10 nondiabetic (8 women, 2 men) offspring of NIDDM patients as defined by the National Diabetes Data Group criteria (15). To ensure ascertainment of the disease, one or both parents of the offspring had NIDDM and were receiving an antidiabetic drug (oral sulfonylurea agent or insulin) at the time of the study. Except for one subject who had two parents with diabetes, all the offspring had one parent with diabetes. Ten healthy subjects (8 women, 2 men) with no family history of diabetes served as control subjects. The control subjects were recruited only if their parents were >50 yr of age and had no diabetes or family history of the disease. These criteria were used empirically to ensure that the likelihood of any of the control subjects developing NIDDM was minimal. The offspring and control subjects were matched for age, sex, and body mass index (BMI). The offspring and control subjects were mostly from the same socioeconomic background. Subjects who participated in competitive and endurance athletic programs or were receiving any medication known to influence glucose metabolism were excluded. In addition, we excluded subjects with cardiac, hepatic, renal, and thyroid disease as assessed by a thorough history, physical examination, and, where necessary, appropriate laboratory testing. Because essential hypertension (blood pressure > 140/90 mmHg) is now considered as an insulin-resistant state by some authorities, such patients were also excluded from the study. Each subject gave a written informed consent approved by the Human Subjects Research Review Committee of The Ohio State University after the risk involved in the study was carefully and thoroughly explained.

Subjects were instructed to include ≥250 g carbohydrate in their diet for 3 consecutive days before the day of the study. All subjects were admitted to the Clinical Research Center on the morning of the study after a 10- to 12-h overnight fast. Metabolic studies were performed on different days separated by 2–4 wk.

Anthropometric measurements. Body weight and height were measured with the participants wearing only an examination gown. The BMI was calculated as weight (kg) divided by height squared (m^2). Skin-fold thickness was measured with Lange's callipers from the biceps, triceps, and the subscapular region at the inferior angle of the scapula. The ratio of the subscapular region and triceps skin-fold thickness was taken as the centrality index, a measure of central (truncal) versus peripheral fat distribution. The waist circumference was measured at the level of umbilicus and the hip circumference at the level of greater trochanter. The waist-hip ratio (WHR) was used to express either lower, intermediate, or upper-body fat distribution and obesity. The corresponding arbitrary cutoff points for the WHR were <0.82, 0.82–0.85, and >0.86, respectively. The WHR was not used as a selection criterion during the recruitment period for the study. The lean body mass and body fat mass were determined with bioelectrical impedance analyzer (BIA; model 101, RJL Systems, Detroit, MI). This technique depends on body tissue resistivity, reactance, and height to compute the lean and body fat mass (16,17). The BIA-derived body compositional variables have been cross-validated with the standard body hydrodensitometric methods in healthy adults and obese subjects (17–19).

Oral glucose tolerance tests. After a 10- to 12-h overnight fast, the subjects ingested 75-g oral glucose load (Koladex, Custom, Baltimore, MD) in a total volume of 250 ml over a 2-min period. Blood samples were obtained at 0, 30, 60, 90, 120, 150, and 180 min for serum glucose levels. The diagnoses of normal glucose

tolerance, IGT, and diabetes were based on the National Diabetes Data Group criteria (15). Patients with IGT and indeterminate results were excluded from the study and further analysis. All our subjects had a normal glucose tolerance test.

Frequent-sampling intravenous glucose test (FSIGT). The modified FSIGT was performed with the subject in a supine position (20,21). After a 10- to 12-h overnight fast, four baseline blood samples were obtained at $t = -5, -2, -1$, and 0 min. Intravenous glucose load (0.3 g/kg, 50% dextrose) was administered over 1 min at $t = 0$ min. At $t = 20$ min, intravenous tolbutamide (300 mg; Orinase Diagnostic, Upjohn, Kalamazoo, MI) was also administered over a 1-min period. Blood samples for glucose and insulin were obtained at frequent intervals between $t = 0$ and 180 min as previously described (20). Samples were centrifuged at 4°C and sera were stored at −20°C until assayed.

Serum and urine glucose concentrations were measured by the glucose oxidase method with a glucose autoanalyzer (Beckman, Fullerton, CA). HbA_{1c} was measured by microcolumn cationic chromatographic technique (Isolab, Akron, OH). The normal reference values in our laboratory were 4.5–8.5%.

Serum insulin levels were measured by standard double-antibody radioimmunoassay techniques. The lower limit of sensitivity for insulin levels was 18 pM. The intra- and interassay coefficients of variation of insulin assay were 6 and 10%, respectively.

Statistical analyses. The sample size was calculated at the significance level of $\alpha = 0.05$ and probability $(1 - \beta)$ of 0.9 to detect ≥25% difference in S_I between the offspring and control subjects. Results are means ± SE unless otherwise stated. The acute first-phase insulin release was taken as the sum of incremental insulin levels between $t = 0$ and 5 min after intravenous glucose and between $t = 20$ and 25 min after tolbutamide administration. The incremental integrated areas under the glucose and insulin curves were determined by the trapezoidal rule. The glucose disappearance rate (K_g) during the intravenous glucose tolerance test was calculated as the slope of the regression line between glucose (after natural log transformation) on the ordinate and time on the abscissa during $t = 8–20$ min in each subject. The S_I and S_G parameters were calculated with the MINIMOD software program (copyright R. Bergman). Because S_G reflects the ability of glucose to mediate its own disposal and suppress basal hepatic glucose production at basal insulin levels (glucose effectiveness), we calculated glucose effectiveness at 0 insulin as $S_G - S_I \times BI$, where BI is basal insulin level. Body fat content and lean body mass were calculated with the BIA software program with modified equations of Segal et al. (19). Multiple and stepwise linear regression and correlation coefficients were calculated by the least-squares method. Statistical analyses were performed by unpaired Student's t test, Mann-Whitney U test, and, where appropriate, analysis of variance (ANOVA) for repeated measures with post hoc testing by the Bonferroni method (SAS statistical program). $P < 0.05$ was considered statistically significant.

RESULTS

The clinical characteristics of the subjects are shown in Table 1. Mean age, body weight, and BMI were not significantly different. Similarly, the anthropometric variables that included WHR, sum of the three skin-fold thicknesses, and subscapular/triceps skin-fold thickness ratios (centrality index) were also not significantly different. The mean lean body mass and percent lean body mass were also not different. In contrast, the body fat mass and percent fat mass were significantly greater ($P < 0.05$) in the offspring compared with the control subjects.

Serum glucose and insulin concentrations. Mean fasting serum glucose levels were significantly greater in the offspring than the control subjects (4.39 ± 0.17 vs. 3.94 ± 0.17 mM, $P < 0.05$). After intravenous glucose administration, mean serum glucose rose to peak levels of 18.50 ± 1.50 and 13.20 ± 1.06 mM ($P < 0.05$) at 2 min in the offspring and control subjects, respectively (Fig. 1). Thereafter, glucose levels declined to a similar nadir, and the mean values were indistinguishable between both groups. Furthermore, the mean K_g values were identical in the two groups (offspring vs. control, 2.17 ± 0.37 vs. 2.20 ± 0.30%/min).

Mean fasting serum insulin levels were twofold greater in the offspring than in the control subjects (64 ± 14 vs. 29 ± 7 pM; Fig.1). However, because of wide variation in basal insulin levels, the difference did

TABLE 1
Clinical characteristics of nondiabetic offspring and healthy control subjects

	Offspring	Control
n (F/M)	8/2	8/2
Age (yr)	28 ± 2	26 ± 2
Black/white	4/6	2/8
Body weight (kg)	66 ± 4	64 ± 3
Height (cm)	164 ± 3	167 ± 3
Body mass index (kg/m²)	25 ± 2	23 ± 0.7
Waist-hip circumference ratio	0.79 ± 0.03	0.75 ± 0.03
Skin-fold thickness (mm)		
Subscapular	16.8 ± 1.2	16.2 ± 2.1
Biceps	15.1 ± 2.3	14.5 ± 1.5
Triceps	18.3 ± 2.2	19.8 ± 2.1
Subscapular/triceps	0.92 ± 0.10	0.82 ± 0.10
Lean body mass (kg)	47.4 ± 7.0	50.0 ± 7.0
Lean body mass (%)	71 ± 3	77 ± 2
Body fat mass (kg)	20 ± 1	15 ± 2*
Body fat mass (%)	27 ± 2	22 ± 2*

Values are means ± SE.
*$P < 0.05$ vs. offspring.

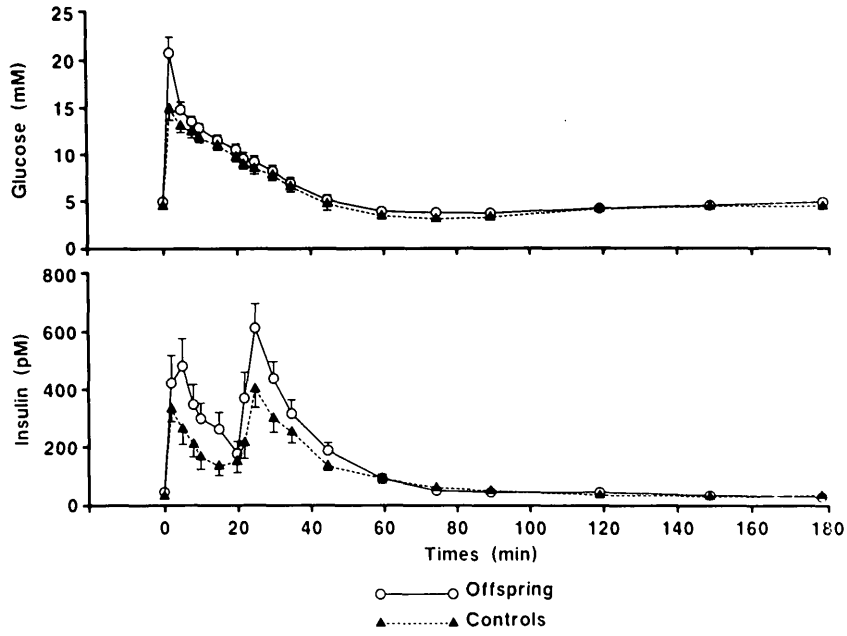

FIG. 1. Mean ± SE serum glucose and insulin concentrations before and during intravenous glucose (0.3 g/kg at t = 0 min) and tolbutamide (300 mg at t = 20 min) tests in offspring and control subjects. Insulin reponses were significantly different ($P < 0.01$) during stimulation by analysis of variance.

not achieve statistical significance. After intravenous glucose administration, mean serum insulin levels rose to significant levels ($P < 0.05$) at 5 min (offspring vs. control, 646 ± 129 vs. 351 ± 72 pM). Between 5 and 20 min, serum insulin levels were again greater in the offspring compared with control subjects. The mean sum of incremental acute first-phase insulin release was greater, but not significantly different, in the offspring than in the control subjects (1127 ± 222 vs. 696 ± 172 pM). After intravenous tolbutamide administration, the mean incremental peak serum insulin levels occurred after 3 min (t = 25 min) in both groups (offspring vs. control, 826 ± 115 vs. 539 ± 86 pM, $P < 0.05$). Mean of the sum of incremental acute first-phase insulin release after intravenous tolbutamide administration was significantly greater ($P < 0.05$) in the offspring than in the control subjects (826 ± 165 vs. 498 ± 85 pM). The serum insulin profiles were significantly different ($P < 0.01$) between the offspring and control subjects by ANOVA. The poststimulation incremental insulin areas were 1.5-fold greater in the offspring than in the control subjects (833 ± 151 vs. 502 ± 86 pM).

S_I and S_G. Modeling could not be performed in one control subject because the integrated insulin area was <1000 planar U. Mean S_I was significantly lower ($P < 0.01$) in the offspring than in the control subjects (4.77 ± 0.67 vs. $8.37 \pm 1.24 \times 10^{-4}$ $min^{-1} \cdot mU^{-1} \cdot L^{-1}$; Fig. 2, *top*). In contrast, S_G was not significantly different between the two groups (offspring vs. control, 1.92 ± 0.12 vs. $2.10 \pm 0.17 \times 10^{-2}$ min^{-1}). Glucose effectiveness at 0 insulin was $1.78 \pm 0.20 \times 10^{-2}$ min^{-1} in offspring and $1.77 \pm 0.16 \times 10^{-2}$ min^{-1} in control subjects.

Disposition index. Because β-cell insulin response bears a reciprocal relationship with peripheral insulin resistance, we used the disposition index $X \times Y$, where X is the S_I, and Y is an acute first-phase β-cell secretory parameter after either intravenous glucose or tolbutamide administration. The disposition index after intravenous glucose administration was not significantly different between the offspring and control subjects (716 ± 138 vs. $662 \pm 153 \times 10^{-4}$ min^{-1}). Similarly, after intravenous tolbutamide administration, the disposition indices were not different (536 ± 98 vs. $510 \pm 64 \times 10^{-4}$ min^{-1}, respectively).

Correlation coefficients between S_I and body compositional and metabolic variables. Figure 3 depicts the relationships between S_I, basal insulin levels, and WHR. S_I correlated significantly but inversely with the basal insulin in the offspring but not in the control subjects. When all subjects were examined as a group, the relationship between S_I and basal insulin levels was slightly weaker ($r = -0.556$, $P < 0.01$) than that of the offspring alone. Furthermore, we found no relationship between S_I and WHR in the offspring, whereas a stronger relationship existed in the control subjects (Fig. 3, *right*). When all the subjects were examined as a group, the relationship tended to be slightly weaker ($r = -0.451$, $P < 0.05$) than in the control subjects alone ($r = 0.632$, $P < 0.05$).

We found a significant negative correlation between S_I and percentage of body fat mass in the offspring ($r = -0.580$, $P < 0.05$) but not in the control subjects (Fig. 4, *left*). In addition, there was a positive relationship between S_I and lean body mass in the offspring but not in the control subjects (Fig. 4, *right*). As a group, we found no significant relationships between S_I and percentage of body fat mass ($r = -0.247$, NS) and percentage of lean body mass ($r = 0.357$, NS). S_I did not correlate with K_g and fasting serum glucose concentrations in any of the groups.

To investigate the interaction of family history and

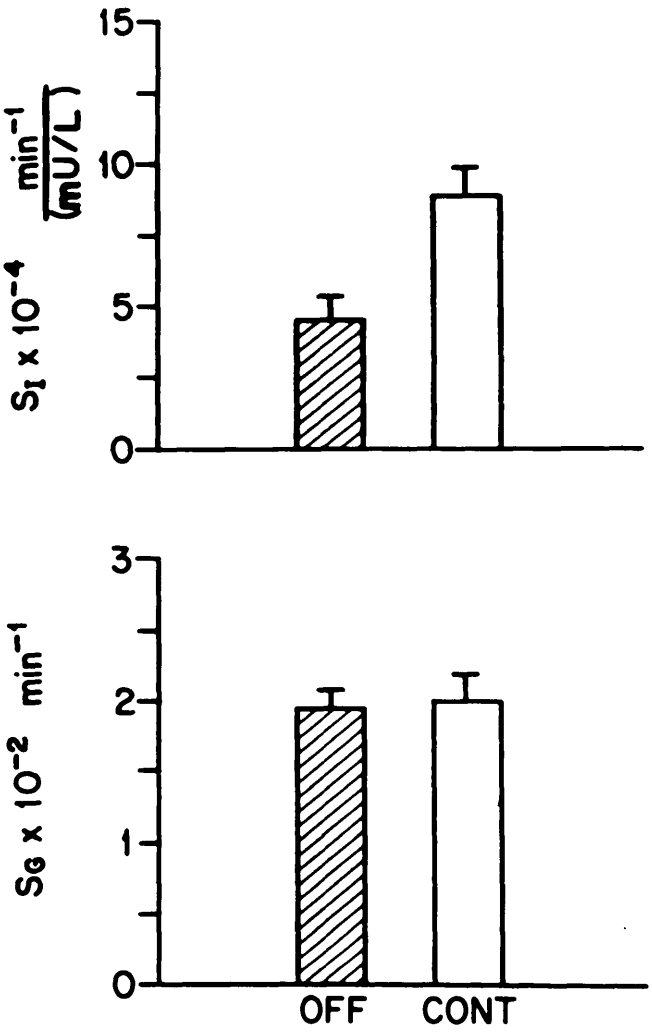

FIG. 2. Mean ± SE insulin sensitivity (S_I) and glucose effectiveness (S_G) in offspring (Off) and control subjects (Cont). $P < 0.01$ (*top*), NS (*bottom*).

anthropometric and metabolic variables with S_I, stepwise linear regression analyses were performed. We found that family history of diabetes and WHR (R^2 = 0.37), sum of skin-fold thickness (R^2 = 0.36), basal insulin (R^2 = 0.37), postglucose peak insulin (R^2 = 0.37), and fasting glucose (R^2 = 0.36) independently explained ~35–38% of the variance in the S_I in our population.

With univariate analyses, family history of diabetes independently accounted for 27% of the variance in the S_I. Similarly, basal and peak insulin accounted for 22.5 and 21.8% of the variance in S_I, respectively. However, unlike the bivariate analyses, sum of skin-fold thickness alone accounted for only 7% of the variance in the S_I in our study groups.

CONCLUSIONS

Studies in first-degree relatives of NIDDM patients have identified an increased prevalence of subtle metabolic

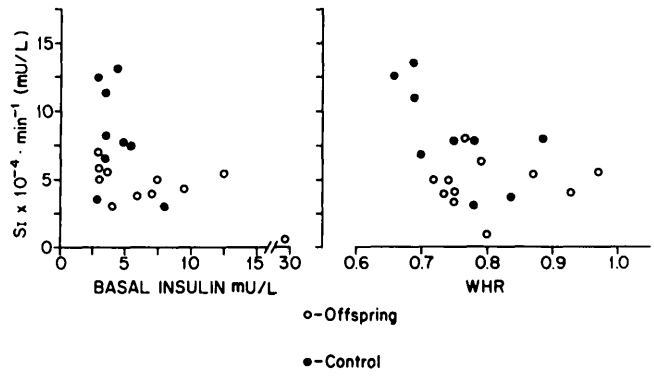

FIG. 3. Relationships between insulin sensitivity (S_I) and basal insulin (*left*) and waist-hip ratio (WHR; *right*) in offspring and control subjects. Basal, $r = -0.798$, $P < 0.01$ for offspring and $r = -0.449$, NS for control; WHR, $r = -0.019$, NS for offspring and $r = -0.632$, $P < 0.02$ for control.

abnormalities, including IGT (11,22), defective splanchnic glucose regulation (4), increased fasting serum glucose and/or insulin levels (4,8,11), and lipoprotein abnormalities (22). In this study, we confirmed the greater fasting and postglucose serum glucose concentrations in the offspring compared with the control subjects, which is in agreement with some previous reports (4,8,11) but not others (5–7). Significantly greater fasting serum glucose occurred in the face of twofold higher peripheral serum insulin levels in the offspring compared with the control subjects. Because fasting serum glucose is predominantly determined by basal hepatic glucose production, it could be inferred that the insulin-mediated regulation of basal hepatic glucose production is impaired or there is increased flux of gluconeogenic precursors to the liver in the offspring.

We found markedly elevated serum insulin levels after both intravenous glucose and tolbutamide administration in the offspring, suggesting an insulin-resistant state. This is in agreement with several previous reports (9–

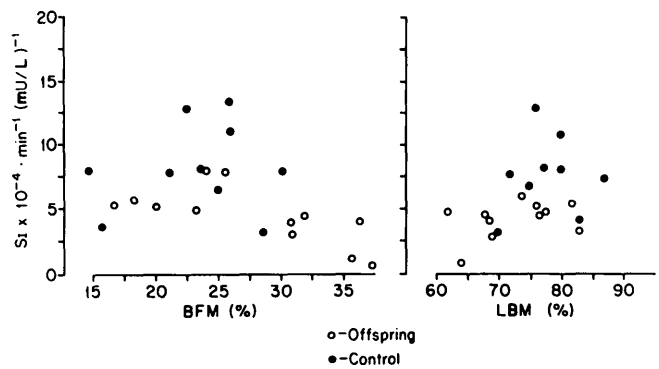

FIG. 4. Relationships between S_I and percentage of body fat mass (BFM; *left*) and lean body mass (LBM; *right*) in offspring and control subjects. BFM, $r = -0.580$, $P < 0.05$ for offspring and $r = -0.449$, NS for control; LBM, $r = 0.593$, $P < 0.05$ for offspring and $r = 0.482$, NS for control.

11,23). With the minimal-model method, we found that the quantitative S_I was remarkably reduced by 45% in the offspring compared with the control subjects. Note that the S_I values found in the control group were similar to those values reported in the literature (13,14). In contrast to our S_I data, Johnson et al. (8), with the minimal-model methodology (FSIGT), found identical S_I values in the offspring of two conjugal diabetic parents compared with control subjects. The reason for the disparate results in our study and that of Johnson et al. (8) is uncertain. Note that, unlike the FSIGT, the modified FSIGT technique (20,21) used in our study has been reported to correlate highly significantly with the euglycemic clamp-derived S_I (24). Recently, Haffner et al. (25) reported 54% reduction in S_I in young nonobese normoglycemic Mexican Americans, a population with a greater prevalence and risk for NIDDM compared with non-Hispanic whites. Indeed, the model parameters in their study were similar to those in our study (offspring vs. Mexican American, S_I 4.77 ± 0.67 vs. 4.06 ± 0.72). In their control group, S_I was 7.56 ± 1.13 compared with 8.37 ± 1.24 in this study. These data from the Mexican Americans who manifest severe insulin-resistant states lend credence to the model-derived data in our offspring.

Previous investigators have reported that S_G is reduced in both NIDDM (13) and IDDM (14) patients. Whether reduced S_G antecedes the development of NIDDM remains uncertain. In this study, glucose effectiveness at basal insulin (S_G) and theoretical zero insulin was not different in both groups; however, there were tremendous interindividual variabilities in both groups. Furthermore, the K_g values, which are often decreased (<1%/min) in poorly controlled diabetic patients and probably reflect predominantly insulin-independent glucose transport, were identical in both groups. Thus, we can infer that the normal glucose tolerance achieved in the insulin-resistant offspring could be partly ascribed to the normal S_G (13).

Previous investigators have shown that upper-body fat distribution or upper-body obesity is associated with an increased prevalence of diabetes, hypertension, hyperinsulinemia, hyperlipidemia, and cardiovascular death (26–30). The upper-body fat distribution assessed by WHR and sum of skin-fold thickness was not significantly different between the two groups in this study. However, we found a greater body fat mass and percentage of body fat content in the offspring than in the control subjects despite the identical body weight and BMI in the two groups. Thus, we surmise that the increased fat content in the offspring is more likely intra-abdominal, i.e., visceral, in location rather than extra-abdominal. Although we used BIA to estimate the body fat and lean masses, the technique has been validated with hydrodensitometrically derived data by several investigators (17–19). Furthermore, there was a strong correlation between the percentage of body fat mass derived by the BIA and that calculated by the formula of Durnin and Womersley (31) based on the skin-fold thickness from at least four sites in our studies. However, validation of the BIA technique in young offspring of NIDDM patients by hydrodensitometry is needed.

This study demonstrated that S_I correlated with percentage of body fat content but not with WHR in offspring, which contrasts with previous studies. In all subjects, S_I correlated positively with the lean body mass, but the effect was more marked in the offspring. We found that the interaction of family history with WHR, sum of skin-fold thickness, basal and postglucose peak insulin, or fasting glucose accounted for ~35–38% of the variance in the S_I in our subjects. However, with univariate analyses, family history of diabetes alone accounted for 27% of the variance in the S_I in our population. Note that Lillioja et al. (32) reported that family membership independently accounted for ~34 and 15% of the variance in the maximum and minimum insulin action, respectively, in nondiabetic Pima Indians during clamp studies.

The mechanisms of the association of S_I and various metabolic and anthropometric variables remain uncertain. Note that previous studies in Pima Indians (32) and Mexican Americans (9,10) have indicated that insulin resistance is a familial trait. Furthermore, Bouchard et al. (33) and several other investigators (34) have reported that body weight and body fat distribution patterns are partly genetically determined. Thus, our findings in offspring could be partly explained on the basis of genetic inheritance. We caution that other variables such as dietary habits and physical activity, not assessed in our study, could have also influenced S_I in our subjects.

In summary, this study demonstrated that normal glucose-tolerant offspring of patients with NIDDM have modestly reduced S_I and greater insulin levels but intact S_G. Our observations further suggest that insulin insensitivity may be causally related to the greater total body fat content and may be genetically determined.

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