Low Insulin Sensitivity ($S_i = 0$) in Diabetic and Nondiabetic Subjects in the Insulin Resistance Atherosclerosis Study

Is it associated with components of the metabolic syndrome and nontraditional risk factors?

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OBJECTIVE — To determine the meaning of $S_i = 0$ derived from the frequently sampled intravenous glucose tolerance test.

RESEARCH DESIGN AND METHODS — The issue of assessing insulin resistance in large studies is important because the most definitive method ("gold standard"), the hyperinsulinemic-euglycemic clamp, is expensive and invasive. The frequently sampled intravenous glucose tolerance test (FSIGTT) has been widely used, but in insulin-resistant subjects (especially diabetic subjects), it yields considerable numbers of subjects whose S_i is zero. The interpretation of an S_i equaling zero is unknown.

RESULTS — To address this issue, we examined 1,482 subjects from the Insulin Resistance Atherosclerosis Study (IRAS) using an insulin-modified FSIGTT and minimal model calculation of S_i. The proportion of insulin-resistant subjects ($S_i < 1.61 \times 10^{-4}$ [$min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$] based on the median of the nondiabetic population) was 38.6% in subjects with normal glucose tolerance (NGT), 74% in subjects with impaired glucose tolerance (IGT), and 92% in subjects with type 2 diabetes. The proportion of subjects with $S_i = 0$ was 2.2% in subjects with NGT, 13.2% in subjects with IGT, and 35.7% in subjects with type 2 diabetes. In subjects with IGT, those with $S_i = 0$ had significantly lower HDL cholesterol levels and higher BMI, waist circumference, fibrinogen, plasminogen-activator inhibitor 1 (PAI-1), C-reactive protein (CRP), and 2-h insulin levels than insulin-resistant subjects with $S_i > 0$. In type 2 diabetes, subjects with $S_i = 0$ had significantly greater BMI and waist circumference and higher triglyceride, PAI-1, CRP, fibrinogen, and fasting and 2-h insulin levels than insulin-resistant subjects with $S_i > 0$. In addition, diabetic subjects with $S_i = 0$ had more metabolic disorders related to the insulin resistance syndrome than diabetic insulin-resistant subjects with $S_i > 0$.

CONCLUSIONS — We found very few subjects with $S_i = 0$ among subjects with NGT and few subjects with $S_i = 0$ among subjects with IGT. In contrast, $S_i = 0$ was common in subjects with diabetes. Subjects with $S_i = 0$ tended to have more features of the insulin resistance syndrome than other insulin-resistant subjects with $S_i > 0$, as would be expected of subjects with almost no insulin-mediated glucose disposal, thus suggesting that subjects with $S_i = 0$ are correctly classified as being very insulin resistant rather than having failed the minimal model program.

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Hyperinsulinemia and insulin resistance have been related to the development of type 2 diabetes (1–7) and cross-sectionally and prospectively with cardiovascular risk factors and atherosclerosis (8–17). Most studies (especially large population-based studies) use surrogates for insulin resistance such as fasting insulin (18) because of the expense and difficulty of direct measures of insulin resistance. In populations in which both insulin levels and insulin resistance have been measured, the latter often has been more closely associated with important clinical outcomes. For example, insulin resistance (as determined by the hyperinsulinemic-euglycemic clamp) was more closely correlated with the development of type 2 diabetes in Pima Indians than was fasting insulin concentration (7). Similarly, insulin resistance (determined by the frequently sampled intravenous glucose tolerance test [FSIGTT]) with minimal model was more closely correlated with atherosclerosis as determined by carotid wall thickness than were insulin concentrations per se in the Insulin Resistance Atherosclerosis Study (IRAS) (17).

The hyperinsulinemic-euglycemic clamp (19), which is the most widely accepted method to assess insulin resistance, is expensive and labor intensive. The FSIGTT has also been used to assess insulin resistance (20,21). A number of modifications have been used to increase

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Abbreviations: CRP, C-reactive protein; FSIGTT, frequently sampled intravenous glucose tolerance test; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; NCEP, National Cholesterol Education Program; NGT, normal glucose tolerance; PAI-1, plasminogen activator inhibitor 1.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

the generalizability of the FSIGTT by the use of insulin injections in diabetic subjects (22) and reducing the number of blood samples required (n = 12) (23). Nevertheless, the use of this technique resulted in a number of subjects whose calculated S_i = 0 by the minimal model computer program in more insulin-resistant subjects, especially diabetic subjects. In a small group of subjects (n = 55), Saad et al. (24) described the prevalence of S_i = 0 (type 2 diabetes: 50% [12/24]; impaired glucose tolerance [IGT]: 15% [3/20]; normal glucose tolerance [NGT]: 0% [0/11]) using an insulin-modified protocol with 12 time points. A number of explanations for the S_i = 0 are possible. The first is that these subjects are, indeed, very insulin resistant with insulin sensitivity not distinguishable from zero. A second possibility is that the use of a one-compartment model (25) may underestimate the S_i, although this interpretation was not supported in other studies (26). Another possibility is that the FSIGTT may yield lower estimates of glucose disposal than the clamp because of the use of a short-acting bolus with its consequent high peak of insulin (27) rather than hyperinsulinemia of long duration, as with the clamp (28).

We have shown that cardiovascular risk factors are increased in insulin-resistant diabetic subjects relative to insulin-sensitive diabetic subjects (29). In this report, we examined whether insulin-resistant diabetic subjects with S_i = 0 have increased metabolic syndrome risk factors relative to insulin-resistant subjects with $S_i > 0$. To examine this issue, we first elucidated the frequency of S_i = 0 in the IRAS, a population-based study of cardiovascular risk factors and insulin sensitivity (30). Next, we characterized all the subjects as insulin resistant or insulin sensitive by using the median for S_i in the nondiabetic population, as had been done previously (31,32). We then evaluated whether subjects with S_i = 0 had more features associated with the insulin resistance syndrome (hyperinsulinemia, obesity, upper-body adiposity, increased dyslipidemia, hypertension, and impaired fibrinolysis and enhanced coagulation) than other insulin-resistant subjects (subjects with $S_i > 0$ but less than the median for S_i in nondiabetic subjects). These analyses are presented separately by glucose tolerance status.

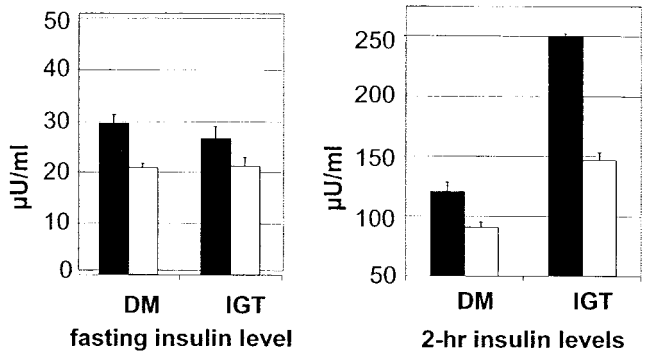

Figure 1—*Mean insulin levels and standard errors adjusted for age, sex, and ethnicity in IGT and diabetes.* ■, S_i = 0; □, $0 < S_i < 1.61$.

RESEARCH DESIGN AND METHODS

— A detailed description of the design and methods of the IRAS has been published (30). In brief, this study was conducted at four clinical centers: Oakland and Los Angeles, California; San Antonio, Texas; and San Luis Valley, Colorado. Diabetic subjects on insulin were not eligible for the IRAS. Of all eligible subjects contacted, 48% completed the 2-day IRAS examination. Diabetic subjects with a fasting glucose level ≥300 mg/dl (≥16.7 mmol/l) were excluded.

A total of 1,625 individuals participated in the IRAS (56% women) (30). Individuals with NGT comprised the largest segment of the study sample (44%) (non-Hispanic white, n = 291; African American, n = 187; and Hispanic, n = 241), followed by those with diabetes (33%) (non-Hispanic white, n = 177; African American, n = 176; and Hispanic, n = 241) and those with IGT (23%) (non-Hispanic white, n = 145; African American, n = 101; and Hispanic, n = 123). The distribution of insulin sensitivity has been recently described in nondiabetic subjects (31) and diabetic subjects (32) from the IRAS.

Height, weight, and girths (minimum waist, waist at the umbilicus and hips) were measured following a standardized protocol. BMI (weight/height^2 [kg/m^2]) was used as an estimate of overall adiposity. Waist circumference was taken as the minimum circumference between the thorax and the hips. The waist circumference was used as an estimate of body fat distribution (30).

The IRAS examination required two visits (~1 week apart [range 2–28 days]) (30–32), each lasting ~4 h. An oral glucose tolerance test and FSIGTT were performed during the first and second visits, respectively. Glucose tolerance was classified according to the World Health Organization criteria (33).

Resting systolic blood pressure and fifth-phase blood pressure were measured three times, and the second and third measurements were averaged. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication.

Insulin resistance was assessed by the FSIGTT (20) with minimal model analyses (34). Two modifications of the original protocol were used. An injection of insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin resistance across a broad range of glucose tolerance (22). This was necessary because of the blunted or absent insulin response in diabetic subjects. Also, the reduced sampling protocol (which required 12 rather than 30 plasma samples and shows similar results to the full protocol [23]) was used because of the large number of subjects. Glucose in the form of a 50% solution (0.3 g/kg) and regular human insulin (0.03 units/kg) were injected through an intravenous line at 0 and 20 min, respectively. Blood was collected at −5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min for plasma glucose and insulin concentrations. S_i was calculated by mathematical modeling methods using the MINMOD program (version 3.0 [1994]). This modified version of the FSIGTT protocol used in the IRAS has been compared with the hyperinsulinemic-euglycemic clamp (24). Acute insulin response was calculated as the increase in insulin concentrations at 2–8 min above the basal (fasting) insulin level.

Plasma glucose was measured with

the glucose oxidase technique on an automated autoanalyzer (Yellow Springs Instruments). Insulin was measured using the dextran-charcoal radioimmunoassay, which has considerable cross-reactivity with proinsulin.

Plasma lipoprotein measurements were obtained from fasting single fresh plasma samples using the Lipid Research Clinic methods. VLDL was isolated by preparative ultracentrifugation, and VLDL (top) and bottom fractions were measured for cholesterol and triglyceride concentrations. HDL cholesterol was measured after precipitation of apolipoprotein B–containing lipoproteins with $MnCl_2$ and heparin. The cholesterol content in the supernatant was measured in a separate autoanalyzer channel set to measure low cholesterol values. LDL cholesterol was calculated as the difference between the HDL cholesterol and the directly measured VLDL bottom cholesterol. Triglycerides were measured enzymatically after correction for free glycerol.

LDL size distribution (i.e., distribution of diameter of the major LDL peak for each participant) was determined using the method of Krauss and Burke (35). Gradient gels were obtained from Isolab (Akron, OH). Measurement of the size of the predominant peak was calibrated using LDL subfractions, the molecular diameter of which was determined by analytical ultracentrifugation (courtesy of Dr. R. Krauss, Donner Laboratories, Berkeley, CA). The LDL size of the predominant peak for an individual was defined as that person's LDL size (36).

Fibrinogen was measured in citrated plasma with a modified clot-rate assay using the Diagnostica STAGO ST4 instrument, as described elsewhere (37). This was based on the original method of Clauss (38) with an internal coefficient of variation (CV) of 3.0%. Plasminogen activator inhibitor 1 (PAI-1) was also measured in citrated plasma (39), using a two-site immunoassay that is sensitive to free PAI-1 but not to PAI-1 complex with tissue plasminogen activator (t-PA) (40); the internal CV was 6.0%. The citrate sample was centrifuged for a minimum of 30,000*g* per minute to make certain that there was no contamination from platelet PAI-1. C-reactive protein (CRP) was measured using an in-house ultrasensitive competitive immunoassay (antibodies and antigens from Calbiochem, La Jolla, CA) with an interassay CV of 8.9% (41).

Mean values of the cardiovascular risk factors were compared according to insulin sensitivity by ANCOVA (SAS version 6.08; SAS Institute, Cary, NC). Logarithmic transformations (for statistical testing) were used for triglyceride, VLDL cholesterol, VLDL triglyceride, and PAI-1. Further adjustment was made for waist circumference. Because waist circumference and BMI were highly correlated ($r = 0.82$), they were not included in the same regression model. Adjustment for waist-to-hip ratio rather than for waist circumference yielded similar results. We preferred to present data for waist circumference rather than waist-to-hip ratio to provide a better measure of visceral adiposity (42). We initially presented our data separately by ethnic group. Using multiple linear regression, we tested for

Table 1—*Distribution of clinical characteristics of subjects by glucose tolerance status (including both insulin-resistant and insulin-sensitive subjects)*

	NGT	IGT	Type 2 diabetes
n	671	332	479
S_i ($\times 10^{-4}$ [$min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$])	2.62 ± 0.41	1.26 ± 0.52	0.55 ± 0.32
$S_i = 0$	15 (2.2)	44 (13.2)	172 (35.7)
$S_i < 1.61$ (insulin resistant)	259 (38.6)	246 (74.0)	442 (92.0)

Data are *n*, means ± SD, or *n* (%).

Table 2—*Clinical characteristics of insulin-resistant diabetic subjects by $S_i = 0$ or $S_i > 0$ ($0 < S_i < 1.61$) adjusted for age, sex, ethnicity, and clinic*

	$S_i = 0$	$0 < S_i < 1.61$	*P*
n	172	270	
Age (years)*	56.6 ± 0.7	57.2 ± 0.5	0.51
Ethnicity* (% W/AA/H)	36/30/34	31/34/35	0.60
Sex* (% female)	59	52	0.13
BMI (kg/m^2)	32.7 ± 0.4	31.0 ± 0.3	0.004
Waist circumference (cm)	102.5 ± 0.9	98.2 ± 0.7	<0.001
Waist-to-hip ratio (cm)	0.92 ± 0.01	0.91 ± 0.01	0.11
Cholesterol (mg/dl)			
Total	212.1 ± 3.5	215.9 ± 2.5	0.37
HDL	39.1 ± 0.8	40.8 ± 0.7	0.12
LDL	138.7 ± 2.7	143.8 ± 35.6	0.17
Triglyceride (mg/dl)	210.0 ± 16.5	177.7 ± 6.7	0.039
LDL size (Å)	257.5 ± 0.6	265.4 ± 0.8	0.25
PAI-1 (ng/ml)	38.5 ± 2.2	29.8 ± 1.2	<0.001
Fibrinogen (mg/dl)	307.5 ± 5.0	288.2 ± 3.6	0.002
CRP (mg/l)‡	3.86 ± 0.30	2.83 ± 0.17	0.001
Glucose (mg/dl)			
Fasting	172.1 ± 4.2	175.4 ± 3.8	0.51
2-h	313.2 ± 7.0	315.3 ± 5.7	0.87
Insulin (μU/ml)			
Fasting	29.7 ± 1.5	21.0 ± 0.7	<0.001
2-h	120.7 ± 8.1	91.0 ± 4.8	<0.001
S_i ($\times 10^{-4}$ [$min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$])	0.00†	0.62 ± 0.02	<0.001
Acute insulin response ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	7.45 ± 2.5	6.85 ± 1.1	0.74
Blood pressure (mmHg)			
Systolic	127.3 ± 1.15	126.9 ± 0.91	0.81
Diastolic	78.4 ± 0.69	78.1 ± 0.54	0.72
Hypertension prevalence* (%)	57	50	0.14

Data are means ± SD unless otherwise indicated. *Variables not adjusted for age, sex, ethnicity, and clinic; †by definition; ‡log-transformed and back-transformed for presentation. AA, African American; H, Hispanic; W, non-Hispanic white.

Table 3—*Clinical characteristics of insulin-resistant diabetic subjects by S_i or $S_i > 0$ ($0 < S_i < 1.61$) adjusted for age, sex, ethnicity, clinic, and waist circumference*

	$S_i = 0$	$0 < S_i < 1.61$	*P*
Cholesterol (mg/dl)			
Total	210.7 ± 3.4	216.1 ± 2.8	0.210
HDL	38.9 ± 0.8	40.5 ± 0.6	0.120
LDL	136.4 ± 2.8	158.7 ± 1.0	0.05
Triglyceride (mg/dl)	212.9 ± 11.8	180.1 ± 9.2	0.19
LDL size (Å)	256.4 ± 0.7	257.5 ± 0.6	0.22
PAI-1 (ng/ml)	36.9 ± 1.7	30.3 ± 1.3	0.004
Fibrinogen (mg/dl)	299.9 ± 4.5	290.0 ± 3.5	0.15
CRP	3.56 ± 0.26	2.94 ± 0.17	0.035
Glucose (mg/dl)			
Fasting	171.7 ± 4.6	175.4 ± 3.6	0.53
2-h	314.9 ± 6.8	312.7 ± 5.3	0.80
Insulin (μU/ml)			
Fasting	28.6 ± 1.1	21.6 ± 0.9	<0.001
2-h	87.6 ± 0.1	64.1 ± 1.1	<0.001
Acute insulin response ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	7.1 ± 1.5	7.0 ± 1.2	0.25
Blood pressure (mmHg)			
Systolic	127.2 ± 0.91	126.9 ± 1.2	0.19
Diastolic	77.9 ± 0.69	78.2 ± 0.54	0.28
Hypertension prevalence (%)	67.2	58.7	0.09

Data are means ± SD unless otherwise indicated.

the interaction of $S_i = 0$ by ethnicity in insulin-resistant subjects. We found no evidence of significant interactions, suggesting that the effect of $S_i = 0$ on cardiovascular risk factors and adiposity was similar in each ethnic group. We also tested for the interaction of sex × $S_i = 0$; again, these interactions were not significant. Therefore, we present data pooling the ethnic groups and both sexes. *P* values for dichotomous or categorical variables were calculated by the χ^2 test. The prevalence of the National Cholesterol Education Program (NCEP) (43) definition of the metabolic syndrome in relation to $S_i = 0$ or $S_i > 0$ in subjects with IGT or diabetes was calculated (Fig. 1). *P* values were calculated by χ^2.

RESULTS — Table 1 shows the distribution of S_i by glucose tolerance status. The mean S_i ($\times 10^{-4}$ [$min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$]) was 2.62 ± 0.32 in subjects with NGT, 1.26 ± 0.52 in subjects with IGT, and 0.55 ± 0.01 in subjects with type 2 diabetes ($P < 0.001$). The proportion of subjects who were insulin resistant (S_i <1.61, median for S_i in nondiabetic subjects) was 38.6% in subjects with NGT, 74.0% in subjects with IGT, and 92.0% in subjects with type 2 diabetes. The number of subjects with $S_i = 0$ was 2.2% in subjects with NGT, 13.2% in subjects with IGT, and 35.7% in subjects with type 2 diabetes. Because few subjects with NGT had $S_i = 0$, subjects with NGT will not be considered further in this article. The remainder of this article will consider insulin-resistant subjects with IGT (n = 246) and type 2 diabetes (n = 442). We will consider whether subjects with $S_i = 0$ are different from subjects with $S_i > 0$ in terms of variables related to the metabolic syndrome.

Table 2 shows levels of anthropometric and cardiovascular risk factors among insulin-resistant type 2 diabetic subjects according to whether they have $S_i = 0$ or $S_i > 0$ adjusted for age, sex, ethnicity, and clinic. Subjects with $S_i = 0$ had significantly greater BMI, waist circumference, triglyceride, PAI-1, fibrinogen, CRP, and fasting and 2-h insulin levels than subjects with $S_i > 0$. Table 3 shows similar data after further adjustment for waist circumference. Subjects with $S_i = 0$ continued to have significantly greater PAI-1, CRP, and fasting and 2-h insulin levels (Fig. 1) than subjects with $S_i > 0$, al-

Table 4—*Clinical characteristics of insulin-resistant subjects with IGT according to whether $S_i = 0$ or $S_i > 0$ ($0 < S_i < 1.61$) adjusted for age, sex, ethnicity, and clinic*

	$S_i = 0$	$0 < S_i < 1.61$	*P*
n	44	202	
Age (years)*	51.5 ± 1.1	56.1 ± 0.8	0.724
Sex* (% female)	59	59	0.98
Ethnicity* (% W/AA/H)	39/27/34	34/29/38	0.82
BMI (kg/m^2)	34.3 ± 1.1	31.1 ± 0.5	0.007
Waist circumference (cm)	103.5 ± 2.0	97.0 ± 0.9	0.004
Waist-to-hip ratio	0.90 ± 0.01	0.88 ± 0.001	0.12
Cholesterol (mg/dl)			
Total	207.7 ± 4.6	215.0 ± 2.6	0.17
HDL	38.8 ± 1.7	44.6 ± 1.0	0.004
LDL	144.2 ± 4.7	142.1 ± 2.6	0.70
Triglyceride (mg/dl)	160.1 ± 1.5	165.8 ± 7.0	0.71
LDL size (Å)	258.9 ± 0.7	259.7 ± 1.5	0.98
PAI-1 (ng/ml)	29.5 ± 2.6	28.2 ± 1.7	0.69
Fibrinogen (mg/dl)	314.2 ± 8.8	283.1 ± 4.0	0.002
CRP (mg/l)	2.94 ± 0.17	2.45 ± 0.20	0.001
Glucose (mg/dl)			
Fasting	107.3 ± 1.6	105.3 ± 0.7	0.27
2-h	170.5 ± 2.7	164.6 ± 1.2	0.05
Insulin (μU/ml)			
Fasting	26.5 ± 2.5	21.3 ± 1.6	0.08
2-h	250.0 ± 2.7	146.4 ± 7.0	<0.001
Acute insulin response ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	50.7 ± 6.7	43.9 ± 3.2	0.36
Blood pressure (mmHg)			
Systolic	125.7 ± 2.7	125.1 ± 1.3	0.85
Diastolic	80.4 ± 1.3	78.8 ± 0.63	0.28
Hypertension prevalence* (%)	41	47	0.50

Data are means ± SD unless otherwise indicated. *Variables not adjusted for age, sex, ethnicity, and clinic. A, African American; H, Hispanic; W, non-Hispanic white.

Table 5—*Clinical characteristics of insulin-resistant subjects with IGT according to $S_i = 0$ or $S_i > 0$ ($0 < S_i < 1.61$) adjusted for age, clinic, ethnicity, sex, and waist circumference*

	$S_i = 0$	$0 < S_i < 1.61$	*P*
Age (years)	56.1 ± 0.6	57.5 ± 1.1	0.267
Cholesterol (mg/dl)			
Total	207.7 ± 4.4	215.0 ± 2.6	0.171
HDL	38.8 ± 1.7	44.6 ± 1.0	0.004
LDL	144.2 ± 4.7	142.1 ± 36.2	0.662
Triglyceride (mg/dl)	165.8 ± 7.0	160.1 ± 13.6	0.707
LDL size (Å)	258.9 ± 0.7	259.7 ± 1.5	0.635
PAI-1 (ng/ml)	29.5 ± 2.6	28.2 ± 1.7	0.686
Fibrinogen (mg/dl)	314.2 ± 8.8	283.1 ± 4.0	0.002
CRP (mg/l)	3.70 ± 0.62	2.48 ± 0.19	0.019
Glucose (mg/dl)			
Fasting	107.3 ± 1.6	109.5 ± 0.7	0.277
2-h	170.5 ± 2.7	164.6 ± 1.2	0.053
Insulin (μU/ml)			
Fasting	26.5 ± 2.5	21.3 ± 1.6	0.081
2-h	250.0 ± 29.0	146.4 ± 7.0	0.001
Acute insulin response ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	50.7 ± 6.7	43.9 ± 3.2	0.367
Blood pressure (mmHg)			
Systolic	124.8 ± 2.7	125.3 ± 1.28	0.86
Diastolic	79.8 ± 1.3	78.8 ± 0.63	0.51
Hypertension prevalence (%)	62.2	49.7	0.18

Data are means ± SD unless otherwise indicated.

though the differences were considerably attenuated.

Table 4 shows the levels of anthropometric and cardiovascular risk factors among insulin-resistant IGT subjects according to whether they had $S_i = 0$ or $S_i > 0$. Subjects with $S_i = 0$ had significantly higher BMI and waist circumference, 2-h insulin, fibrinogen, and CRP levels and lower HDL cholesterol levels than subjects with $S_i > 0$. After further adjustment for waist circumference, subjects with $S_i = 0$ continued to have significantly greater 2-h insulin, CRP, and fibrinogen levels and lower HDL cholesterol levels than subjects with $S_i > 0$ (Table 5).

Figure 1 shows an analysis of clustering of variables related to the metabolic syndrome according to whether subjects had $S_i = 0$ or $S_i > 0$. Five factors were identified: *1*) high triglyceride, *2*) upper-body adiposity (high waist circumference), *3*) fasting ≥110 mg/dl, *4*) low HDL cholesterol, and *5*) hypertension. The cut points were based on the NCEP criteria for the metabolic syndrome (45). Individuals could have zero to four disorders. In both subjects with IGT and subjects with type 2 diabetes, those with $S_i = 0$ had a shift to more metabolic disorders than those with $S_i > 0$, although these results were significant only for the type 2 diabetic subjects. The prevalence of the NCEP metabolic syndrome in IGT subjects was 51.2% in subjects with $S_i = 0$ compared with 46.6% in subjects with S_i: $0 < S_i < 1.61$ (NS) (Fig. 2). The prevalence of the NCEP metabolic syndrome in diabetic subjects with $S_i = 0$ was 85.2% compared with 70.8% in subjects with S_i: $0 < S_i < 1.61$ ($P < 0.001$).

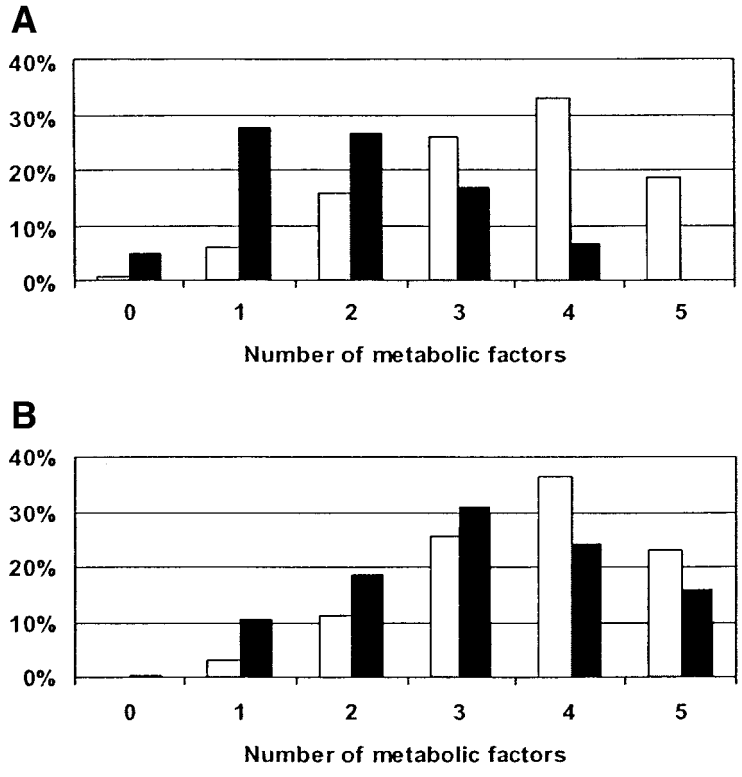

**Figure 2—*Relation of numbers of metabolic disorders (0–5) in relation to $S_i = 0$ or $S_i > 0$ in insulin-resistant subjects.* A: *All subjects.* B: *Diabetic subjects.* P *values were calculated by* χ^2. *Metabolic disorders were defined by the NCEP criteria (43).* □, $S_i = 0$ (n = *231);* ■, $0 < S_i < 1.61$ (n = *716);* P < *0.0001.*

CONCLUSIONS — Among a group of subjects with insulin resistance (defined by $S_i < 1.61 \times 10^{-4}$ [$min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$] based on the median in the nondiabetic population), we have shown that subjects with IGT and type 2 diabetes with $S_i = 0$ are significantly more obese (as determined by BMI) and have greater upper-body adiposity (as determined by waist circumference) than subjects with $0 < S_i < 1.61$. (This was also true of subjects with NGT, although the number of subjects with $S_i = 0$ was very small [*n* = 15] and therefore not shown in the tables.) We have also shown that subjects with $S_i = 0$ have increased cardiovascular risk factors compared with subjects with $S_i > 0$, although the results were not com-

pletely consistent in the IGT and type 2 diabetic subjects (lipids: type 2 diabetes [increased triglyceride] vs. IGT [decreased HDL cholesterol]; fibrinolysis/coagulation: type 2 diabetes [increased PAI-1 and fibrinogen and subclinical inflammation, increased CRP in both type 2 diabetes and IGT] vs. IGT [increased fibrinogen]). Blood pressure did not differ in insulin-resistant subjects with $S_i = 0$ vs. $S_i > 0$. Lastly, subjects with $S_i = 0$ had higher fasting and 2-h insulin concentrations than subjects with $S_i > 0$, in both IGT and type 2 diabetes. The differences between subjects with $S_i = 0$ and $S_i > 0$ were only partially associated with the increased upper-body adiposity in subjects with $S_i = 0$ (Tables 3 and 5). Additionally, subjects with $S_i = 0$ had higher insulin concentrations after further adjustments for the small differences in the glucose concentrations between $S_i = 0$ and $S_i > 0$ subjects (data not shown). Taken together, these findings indicate that subjects with S_i values indistinguishable from zero were more insulin resistant than their insulin-resistant counterparts with $S_i > 0$. These results are reinforced by the evidence of greater clustering of cardiovascular risk factors in diabetic subjects with $S_i = 0$ than in subjects with $S_i > 0$, and a higher prevalence of the metabolic syndrome defined by the NCEP (Fig. 1). These results were significant in diabetic subjects but not in subjects with IGT possibly because of the much lower number of IGT subjects with $S_i = 0$ than diabetic subjects with $S_i = 0$ ($n = 44$ vs. 172) (Fig. 2).

Because laboratory procedures such as the glucose clamp are not practical in a large study, we used the minimal model. Strong correlations between S_i from the minimal model and glucose disposal rate from the clamp have been reported in several studies (24). In normal subjects, interpretable measurements of S_i were derived from the insulin-boosted FSIGTT. However, in IRAS, we discovered in some IGT subjects (13.2%) and in many participants with type 2 diabetes (35.7%) that it was not possible to calculate a value of S_i from the MINMOD software that was distinguishable from 0. The purpose of the present analysis was to examine characteristics of subjects with S_i not distinguishable from 0; we could note these values of S_i as "$S_i \sim 0$" for ease of discussion.

Our data lend support to the notion that zero S_i values obtained from minimal model analysis of the insulin-modified FSIGTT represent a lack of a discernable effect of the injected amount of insulin on plasma glucose. To clarify this issue further, it is necessary to recapitulate the approach used to estimate S_i with the minimal model approach. The MINMOD program examines the moment-to-moment effect of the changes in insulinemia on plasma glucose and calculates a value for S_i. The insulin sensitivity index obtained with this approach is simply the steady-state effect of an incremental change in plasma insulin to increase fractional glucose disappearance independent of glycemia. In extremely insulin-resistant subjects, the injected amount of insulin (~2 units in the current study) fails to produce a discernable change in glucose utilization. Consequently, the model cannot assign a finite value to S_i and a zero value is obtained.

Therefore, the MINMOD $S_i = 0$ values appear to identify a group of subjects (mostly type 2 diabetic patients) in whom insulin-mediated glucose disposal is very low. The existence of such very insulin-resistant subjects is supported by DeFronzo et al. (19), who showed that insulin infusion during the clamp at a rate of 40 mU $\cdot$ m^{-2} $\cdot$ min^{-1} (a total dose of ~16 units over 3 h) increased plasma insulin concentrations to 531 ± 102 pmol/l without inducing a significant increase in forearm glucose uptake (5.84 ± 1.51 μmol $\cdot$ min^{-1} $\cdot$ kg^{-1} vs. a basal value of 4.38 ± 1.16). Moreover, Alzaid et al. (44) found that when the plasma insulin pattern normally seen during an oral glucose tolerance test was simulated by an intravenous insulin infusion, while clamping glucose at the basal concentration, the insulin increment had no measurable effect on the glucose utilization rate in type 2 diabetic patients. The total insulin dose infused in the latter study was similar to that used in the insulin-modified FSIGTT with an insulin dose of 0.03 units/kg, viz., ~2 units. These findings suggest that MINMOD $S_i = 0$ values represent a real pathophysiological phenomenon (i.e., a lack of glucose response to an increase in insulin level within the range that occurs with day-to-day food ingestion) that exists in a substantial proportion of some individuals with type 2 diabetes and in a minority of those with IGT or NGT.

The current report of the IRAS on whether $S_i = 0$ subjects are insulin resistant was a retrospective analysis. A more definitive approach to whether $S_i = 0$ subjects are actually very insulin resistant would be to use prospectively the euglycemic-hyperinsulinemic clamps in subjects whose FSIGTT showed an $S_i = 0$. The issue of $S_i = 0$ is most important in diabetic subjects because of the higher prevalence of $S_i = 0$ in this group.

In conclusion, we have shown that subjects with IGT and type 2 diabetes who have $S_i = 0$ are more obese and have increased cardiovascular risk factors linked to the insulin resistance syndrome and greater peripheral hyperinsulinemia than corresponding insulin-resistant subjects with $S_i > 0$. These results suggest that subjects with $S_i = 0$ are, indeed, very insulin resistant and probably represent an S_i very close to zero rather than a failure of the minimal model. Perhaps these subjects might be better described as having insulin sensitivity not distinguishable from 0 ($S_i \sim 0$).

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