

# The Natural Course of $\beta$ -Cell Function in Nondiabetic and Diabetic Individuals

## The Insulin Resistance Atherosclerosis Study

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Data from the UKPDS (U.K. Prospective Diabetes Study) indicate a continuous decline in  $\beta$ -cell function in patients with type 2 diabetes. We studied longitudinal changes in  $\beta$ -cell function (follow-up of 5.2 years) in subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes, using acute insulin response (AIR) and insulin sensitivity index ( $S_i$ ) from a frequently sampled intravenous glucose tolerance test among African-American, Hispanic, and non-Hispanic white subjects aged 40–69 years. At baseline, decreasing levels of both  $S_i$  and AIR (either unadjusted or adjusted for  $S_i$ ) mirrored deteriorating glucose tolerance status at baseline and at follow-up. A different pattern was found with respect to longitudinal changes;  $S_i$  declined in each glucose tolerance category, ranging from  $-0.81 \times 10^{-4} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$  in NGT at baseline and NGT at follow-up (NGT/NGT) to  $-1.06 \times 10^{-4}$  in NGT/diabetes, whereas the directional change in AIR principally determined the glucose tolerance status at follow-up. In NGT/IGT  $S_i$  decreased by 35% and AIR increased by 34%. Results were similar in each of the three ethnic groups. These data shed light on the natural course of  $\beta$ -cell function; over 5.2 years, mean insulin sensitivity declined in each glucose tolerance category. The change in AIR, however, principally determined glucose tolerance status at follow-up; NGT was maintained by a compensatory increase in insulin secretion. Failure to increase insulin secretion led to IGT, and a decrease in insulin secretion led to overt diabetes. This data may have important implications for the prevention and treatment of type 2 diabetes. *Diabetes* 55:1114–1120, 2006

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AIR, acute insulin response; FSGIT, frequently sampled intravenous glucose tolerance test; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; UKPDS, U.K. Prospective Diabetes Study.

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Impaired insulin secretion and impaired insulin action (increased insulin resistance) are the two major components contributing to the pathophysiology of type 2 diabetes (1–3); their complex relationship has been mathematically described as a curvilinear relationship (4–6). Longitudinal studies indicate that compromised  $\beta$ -cell function is detectable in pre-diabetic individuals long before the onset of actual type 2 diabetes (1,7). The natural course of  $\beta$ -cell function over time, however, is poorly understood, and published data are scarce. A longitudinal study in Pima Indians highlighted the importance of declining  $\beta$ -cell function in individuals transitioning from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) and IGT to diabetes, respectively (3). In the U.K. Prospective Diabetes Study (UKPDS), a continuous decline in  $\beta$ -cell function in patients with type 2 diabetes, irrespective of glucose-lowering treatment, was demonstrated (8). No data on the natural course of  $\beta$ -cell function is currently available in a large population, across different ethnic groups, and using a direct measure of insulin secretion. Therefore, we studied longitudinal changes in  $\beta$ -cell function over 5.2 years by acute insulin response (AIR) relative to insulin sensitivity index ( $S_i$ ), as assessed from a frequently sampled intravenous glucose tolerance test (FSIGTT) among African-American, Hispanic, and non-Hispanic white subjects in the Insulin Resistance Atherosclerosis Study (IRAS).

### RESEARCH DESIGN AND METHODS

The IRAS is a multicenter epidemiological study aiming to explore relationships between insulin resistance, cardiovascular risk factors, and disease across different ethnic groups and various states of glucose tolerance. A full description of the design and methods of the IRAS has been published (9). The IRAS protocol was approved by local institutional review committees, and all subjects gave informed consent. A total of 1,624 (nondiabetic and diabetic) individuals participated in the IRAS baseline examination. After an average of 5.2 years (range 4.5–6.6), follow-up examinations were conducted, using the protocol used at baseline. The response rate was 81%, and those who attended the follow-up examination were similar to those who did not attend in terms of ethnicity, sex, baseline glucose tolerance status, and BMI ( $P > 0.32$  for all comparisons). This report includes data in subjects with NGT, IGT, and type 2 diabetes, who were treated nonpharmacologically only, to avoid confounding of the results by concomitant antidiabetic medication. Cross-sectional baseline analyses are shown in the overall cohort ( $n = 1,263$  after excluding 219 diabetic subjects being treated pharmacologically and 142 subjects without data from FSGIT at baseline). Longitudinal analyses are shown in 791 individuals after further excluding subjects without follow-up FSGIT data ( $n = 376$ ), type 2 diabetic patients on glucose-lowering medication at follow-up ( $n = 81$ ), and diabetic subjects whose glucose tolerance status

TABLE 1  
Baseline characteristics

	NGT	<i>P</i>	IGT	<i>P</i>	Type 2 diabetes
<i>n</i>	665	—	317	—	281
Age (years)	53.8 ± 0.3	<0.001	57.1 ± 0.5	0.97	57.1 ± 0.5
Female (%)	52.8	0.017	60.9	0.21	55.9
BMI (kg/m <sup>2</sup> )	27.4 ± 0.2	<0.001	30.4 ± 0.3	0.006	31.7 ± 0.3
Waist (cm)	88.3 ± 0.5	<0.001	95.4 ± 0.7	<0.001	99.3 ± 0.8
Fasting glucose (mg/dl)	95.3 ± 0.9	<0.001	103.7 ± 1.3	<0.001	148.5 ± 1.4
2-h glucose (mg/dl)	105.4 ± 1.5	<0.001	163.2 ± 2.2	<0.001	269.0 ± 2.3
Fasting insulin (μU/ml)*	11.6 ± 0.3	<0.001	15.6 ± 0.6	<0.001	20.2 ± 0.8
<i>S</i> <sub>i</sub> × 10 <sup>-4</sup> (min <sup>-1</sup> · μU <sup>-1</sup> · mL <sup>-1</sup> )*	2.13 ± 0.06	<0.001	1.05 ± 0.06	<0.001	0.46 ± 0.04
AIR (μU/ml)*	54.1 ± 1.6	<0.001	42.9 ± 1.9	<0.001	24.4 ± 1.1
AIR adjusted for <i>S</i> <sub>i</sub> (μU/ml)*	65.0 ± 1.9	<0.001	38.9 ± 1.6	<0.001	17.6 ± 0.8

Data are the means ± SE. *P* values are for test of difference in means of the two adjacent categories. \*Log transformed for analysis and back transformed for presentation.

improved from baseline to follow-up (*n* = 15). Each of the two IRAS examinations required two visits. Patients were asked before each visit to fast for 12 h, to abstain from heavy exercise and alcohol for 24 h, and to refrain from smoking the morning of the examination. Race and ethnicity were assessed by self-report.

A standard 75-g oral glucose tolerance test (OGTT) was performed, and diabetes was defined by the OGTT, using World Health Organization criteria, or by the use of diabetes medication. An FSIGTT (10) with minimal model analysis (11) was performed to assess insulin sensitivity. Two modifications of the original protocol were used. An injection of regular insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance. In addition, the reduced sampling protocol (which required 12 rather than 30 plasma samples) was used because of the large number of subjects. Insulin sensitivity, expressed as the *S*<sub>i</sub>, was calculated by mathematical modeling methods (Minmod, version 3.0 [1994]). AIR was calculated as the mean plasma insulin concentration at 2 and 4 min after the administration of glucose. Height, weight, girth, and laboratory measurements were performed using standard methods, as described previously (6).

**Statistical analyses.** All statistical calculations were performed using SAS version 8.0. Log-transformed values were used for all measures that appeared to be more normally distributed with the transformation than without it. In the case of *S*<sub>i</sub>, *S*<sub>i</sub> + 1 was log transformed because the logarithm of 0, a valid value for *S*<sub>i</sub>, is undefined. In addition, insulin sensitivity and insulin secretion measures were log transformed to fit models conforming to the established curvilinear-shaped relationship within each glucose tolerance category. ANCOVA and ordinary least-squares regression were used to assess the associations at baseline between glucose tolerance, insulin sensitivity, and insulin secretion. We also plotted the regression estimates of the associations between AIR, *S*<sub>i</sub>, and glucose tolerance. Interaction terms for glucose tolerance and main effect and interaction terms for ethnicity were added to regression models to test for significant differences. Longitudinal comparisons were made using ANCOVAs of *S*<sub>i</sub>, AIR (both without and with baseline *S*<sub>i</sub> as an additional predictor), and other metabolic measures by baseline and follow-up glucose tolerance status both pooled and stratified by ethnicity.

## RESULTS

**Cross-sectional analyses at baseline.** At baseline all metabolic variables shown in Table 1 were significantly different between the glucose tolerance categories. As expected, *S*<sub>i</sub> was highest in NGT, intermediate in IGT, and lowest in type 2 diabetes. Both unadjusted AIR and AIR adjusted for *S*<sub>i</sub> showed the same pattern (high in NGT, intermediate in IGT, and low in type 2 diabetes), and adjustment for *S*<sub>i</sub> slightly accentuated the differences between glucose tolerance categories.

**Relation of *S*<sub>i</sub> and AIR stratified by baseline glucose tolerance status and stratified by ethnicity.** Ordinary least-squares regression with AIR as the dependent variable and *S*<sub>i</sub> and glucose tolerance category as independent variables yielded the following model: AIR = β/(*S*<sub>i</sub> +

1)<sup>0.665</sup>, or, equivalently, AIR × (*S*<sub>i</sub> + 1)<sup>0.665</sup> = β, where β = 115.8 if NGT, 69.2 if IGT, and 31.4 if diabetic, *R*<sup>2</sup> = 0.30. The parameter estimate (0.665) for the exponent of *S*<sub>i</sub> + 1 (the coefficient of the natural logarithm of *S*<sub>i</sub> + 1) was significantly different from 1 (*P* < 0.0001). When the 148 subjects with *S*<sub>i</sub> = 0 were excluded from the dataset and log(*S*<sub>i</sub>) was substituted for log(*S*<sub>i</sub> + 1), the estimated exponent parameter was 0.384, further from 1.0 (*P* < 0.001). When added to the initial model, the interaction between glucose tolerance status and *S*<sub>i</sub> was nonsignificant (*P* = 0.96 for IGT and *P* = 0.77 for diabetes). This indicates that the relation of *S*<sub>i</sub> and AIR was not statistically different across glucose tolerance categories; i.e., the regression lines for ln(AIR) on the *y*-axis and ln(*S*<sub>i</sub> + 1) on the *x*-axis ran parallel, differing only in intercept (Fig. 1).

The coefficients of ethnic main effect terms were significant (blacks and Hispanics each *P* < 0.005), and the parameter estimates were β = 98.1 if NGT, 59.2 if IGT, and 27.2 if diabetic for non-Hispanic white subjects (reference group); 117.1, 70.7, and 32.5 for black subjects; and 124.7, 75.3, and 34.6 for Hispanic subjects. Ethnic interaction terms added to the previous model were not significant (*P* = 0.67 for blacks and *P* = 0.40 for Hispanics). These results indicate that the regression lines within each of the

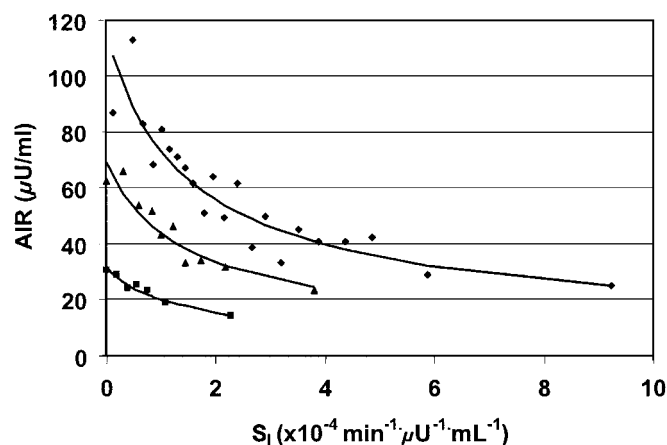


FIG. 1. Relation of β-cell function (first-phase insulin response to intravenous glucose; AIR) and *S*<sub>i</sub> in subjects with NGT (◆), IGT (▲), and type 2 diabetes (diet only) (■) at baseline. The mean AIR levels were plotted against mean *S*<sub>i</sub> levels in quantiles within each glucose tolerance category specified so that ~30 subjects were included in each group.

TABLE 2  
Baseline measures by baseline and follow-up glucose tolerance status

Baseline:	NGT				IGT			
	NGT	P	IGT	Type 2 diabetes	NGT	P	IGT	Type 2 diabetes
n	350		105	40	66		95	76
Age (years)	52.9 ± 0.4	0.077	54.6 ± 0.8	56.6 ± 1.3	56.9 ± 1.0	0.95	56.8 ± 0.9	58.4 ± 1.0
BMI (kg/m <sup>2</sup> )	27.1 ± 0.3	0.55	27.5 ± 0.5	29.4 ± 0.8	29.5 ± 0.6	0.49	30.0 ± 0.5	31.0 ± 0.6
Waist (cm)	87.7 ± 0.6	0.69	88.3 ± 1.2	92.8 ± 1.9	93.4 ± 1.5	0.48	94.8 ± 1.2	97.1 ± 1.4
Fasting glucose (mg/dl)	94.6 ± 0.7	0.51	95.5 ± 1.3	100.2 ± 2.1	101.4 ± 1.7	0.75	102.1 ± 1.4	132.8 ± 1.6
2-h glucose (mg/dl)	102.3 ± 1.4	<0.001	112.8 ± 2.5	119.0 ± 4.1	155.6 ± 3.2	0.049	163.8 ± 2.7	245.7 ± 3.0
HOMA-IR (mmol · μU <sup>-1</sup> · ml <sup>-1</sup> )	3.1 ± 0.2	0.68	3.3 ± 0.4	4.8 ± 0.7	4.1 ± 0.5	0.51	4.6 ± 0.5	7.8 ± 0.5
S <sub>i</sub> × 10 <sup>-4</sup> (min <sup>-1</sup> · μU <sup>-1</sup> · ml <sup>-1</sup> )*	2.31 ± 0.08	0.023	1.94 ± 0.14	1.66 ± 0.21	1.39 ± 0.14	0.052	1.07 ± 0.10	0.47 ± 0.08
AIR (μU/ml)*	59.5 ± 2.5	0.005	46.9 ± 3.6	44.3 ± 5.7	45.5 ± 4.5	0.92	46.1 ± 3.8	26.8 ± 2.5
AIR adjusted for S <sub>i</sub> (μU/ml)*	71.3 ± 2.7	<0.001	51.3 ± 3.5	44.8 ± 5.0	42.2 ± 3.6	0.34	38.1 ± 2.7	17.0 ± 1.5

Data are means ± SE. P values are for test of difference in means of the two adjacent categories. \*Log transformed for analysis and back transformed for presentation. HOMA-IR, homeostasis model assessment of insulin resistance.

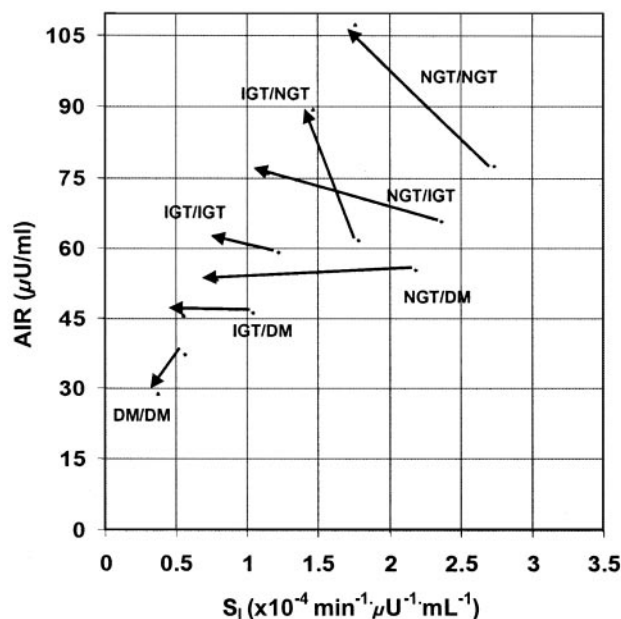


FIG. 2. Changes of S<sub>i</sub> and AIR from baseline (arrow base) to follow-up (arrow top) in populations stratified by baseline and follow-up glucose tolerance status. DM, type 2 diabetes.

three ethnic groups had different intercepts, but that lines ran parallel within each glucose tolerance category.

**Cross-sectional analyses at baseline stratified by baseline and follow-up glucose tolerance status.** Decreasing levels of S<sub>i</sub> and AIR at baseline mirrored deteriorating glucose tolerance status; from NGT/NGT to diabetes/diabetes (columns from left to right on Table 2). Subjects with NGT at baseline who remained so at follow-up (NGT/NGT) had the highest baseline values of S<sub>i</sub>, those who developed IGT (NGT/IGT) had intermediate values, and those who developed type 2 diabetes (NGT/diabetes) had the lowest S<sub>i</sub> values at baseline. A similar pattern (without reaching statistical significance) was found in subjects with IGT at baseline. A similar pattern as for S<sub>i</sub> was found for AIR in relation to baseline and follow-up glucose tolerance status; NGT/NGT had the highest, NGT/IGT had intermediate, and NGT/diabetes had the lowest AIR levels at baseline. Adjustment for S<sub>i</sub> yielded an even more pronounced differentiation between glucose tolerance categories. Finally, as expected, subjects with type 2 diabetes at baseline had lower levels of both S<sub>i</sub> and AIR than any other population.

**Longitudinal analyses stratified by baseline and follow-up glucose tolerance status.** A slightly different pattern was found with respect to longitudinal changes between S<sub>i</sub> and AIR, respectively, in relation to baseline/follow-up glucose tolerance status (Table 3). S<sub>i</sub> declined in each glucose tolerance category, ranging from -0.81 × 10<sup>-4</sup> min<sup>-1</sup> · μU<sup>-1</sup> · ml<sup>-1</sup> in NGT/NGT to -1.06 × 10<sup>-4</sup> in NGT/diabetes; the decline was significantly different between NGT/NGT and NGT/IGT. AIR, by contrast, increased in all categories, except for a minimal decline in NGT/diabetes and diabetes/diabetes. The change in AIR was significantly different between NGT/IGT and NGT/diabetes and between IGT/NGT and IGT/IGT. As in previous models (as shown above), adjustment of AIR for S<sub>i</sub> accentuated these differences. Figure 2 shows a decrease in S<sub>i</sub> in each of the glucose tolerance categories (arrow pointing from right to left), whereas the directional

**TABLE 3**  
Changes in variables of interest by baseline and follow-up glucose tolerance status

Baseline:	NGT			IGT		
	Follow-up:	NGT	P	IGT	P	Type 2 diabetes
ABMI (kg/m <sup>2</sup> )	0.7 ± 0.1	0.25	1.0 ± 0.2	0.30	0.6 ± 0.4	0.3 ± 0.3
ΔWaist (cm)	2.8 ± 0.3	0.29	3.4 ± 0.5	0.56	3.9 ± 0.8	1.5 ± 0.6
ΔFasting glucose (mg/dl)	0.3 ± 0.9	0.064	4.0 ± 1.7	<0.001	22.4 ± 2.8	-2.2 ± 2.2
Δ2-h glucose (mg/dl)	3.2 ± 2.0	<0.001	47.6 ± 3.7	<0.001	110.7 ± 5.9	-35.7 ± 4.6
ΔHOMA-IR (mmol · μU/ml)	0.6 ± 0.3	0.47	1.0 ± 0.5	0.002	3.9 ± 0.8	0.5 ± 0.6
ΔS <sub>i</sub> × 10 <sup>-4</sup> (min <sup>-1</sup> · μU <sup>-1</sup> · ml <sup>-1</sup> )*	-0.81 ± 0.06	0.021	-0.94 ± 0.08	0.12	-1.06 ± 0.11	-0.23 ± 0.11
ΔAIR (μU/ml)*	20.4 ± 2.6	0.40	12.6 ± 3.5	0.028	-0.2 ± 4.3	16.5 ± 4.7
ΔAIR adjusted for S <sub>i</sub> (μU/ml)*	23.7 ± 2.9	0.11	10.4 ± 3.5	0.005	-4.7 ± 3.8	19.6 ± 4.5
						0.007
						5.1 ± 2.6
						0.20
						0.4 ± 2.0
						-1.2 ± 1.1
						0.24
						-0.41 ± 0.08
						0.38
						0.4 ± 2.8
						-0.16 ± 0.06
						-3.4 ± 1.7

Data are means ± SE. P values are for test of difference in means of the two adjacent categories. \*Log transformed for analysis and back-transformed for presentation. HOMA-IR, homeostasis model assessment of insulin resistance.

change in AIR principally determined the glucose tolerance status at follow-up (arrow pointing upwards for NGT; running parallel or slightly upwards for IGT; and running parallel or downwards for type 2 diabetes). In NGT/NGT S<sub>i</sub> decreased by 35%, and AIR increased by 34%. **Analyses stratified by baseline and follow-up glucose tolerance status and by ethnicity.** At baseline, African Americans and Hispanics had higher AIR and lower S<sub>i</sub> compared with non-Hispanic whites (data not shown, previously reported in 11). In longitudinal analyses (Table 4), a similar pattern emerged within each of the three ethnic groups as seen in the overall population (Tables 2 and 3). Statistically significant differences were found for some of the comparisons within strata; relatively low numbers of subjects in some of the strata need to be taken into account. Tests for heterogeneity showed that all comparisons were nonsignificant, except for the change of AIR adjusted for the change in S<sub>i</sub> (P = 0.042). Overall, these analyses indicate that findings in the overall population are consistent across all three ethnic groups of the IRAS.

**DISCUSSION**

The current study yields several novel findings; we report 1) a curvilinear relationship between S<sub>i</sub> and AIR as assessed by a direct measure of insulin resistance, the FSIGTT, in a large population; 2) consistency of this finding across the three ethnic groups of the IRAS and across glucose tolerance categories (including type 2 diabetes); 3) a decline in insulin sensitivity over time; and 4) a change in AIR, which determined glucose tolerance status after 5.2 years.

Based on cross-sectional analyses, we found a curvilinear relation between S<sub>i</sub> and AIR in a large population of three ethnic groups across different glucose tolerance categories, including patients with type 2 diabetes. Because the exponent parameter differed significantly from 1, our models did not conform exactly to the hyperbolic form (AIR × S<sub>i</sub> = a constant). However, they certainly have the nonlinear feature that differences in S<sub>i</sub> among insulin-sensitive subjects are associated with smaller differences in AIR than that among insulin-resistant subjects. Thus, these findings confirm and extend knowledge from previous studies performed in healthy nondiabetic subjects (3–6,12). In the current study, the curvilinear relation was seen across all three ethnic groups of the IRAS, irrespective of prevailing differences in S<sub>i</sub> and AIR across the three ethnic groups (13). In a previous study, β-cell function (as assessed using the insulinogenic index from an OGTT, i.e., the increment of insulin over the increment of glucose adjusted for homeostasis model assessment of insulin resistance) was decreased in relation to the underlying glucose tolerance status in African Americans, Asian Americans, Caucasians, and Hispanic Americans alike (14).

In contrast to the curvilinear relationship, which is based on cross-sectional data, published data on longitudinal changes in β-cell function are scarce. Subjects who transitioned from NGT to IGT gained weight and showed a decline in insulin sensitivity and a decline in AIR (3). In the same study, transition from IGT to diabetes over time was associated with a further increase in body weight; a further decline in insulin sensitivity and AIR, respectively; as well as an increase in basal (hepatic) glucose output. Control subjects, who remained NGT over the entire observational period, also gained weight, but their AIR increased with decreasing insulin sensitivity (3). These

TABLE 4  
Baseline measures and changes in variables of interest by baseline and follow-up glucose tolerance status

Baseline	NGT				IGT				Type 2 diabetes	
	NGT	P	IGT	P	NGT	P	IGT	P		
Follow-up	NGT	P	IGT	P	Type 2 diabetes	P	IGT	P	Type 2 diabetes	
<b>Whites</b>										
<i>n</i>	143	—	43	—	17	—	38	—	24	26
$S_1 \times 10^{-4}$ ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$ )*	2.56 ± 0.15	0.54	2.39 ± 0.25	0.19	1.86 ± 0.33	1.97 ± 0.28	1.14 ± 0.16	0.11	0.79 ± 0.17	0.40 ± 0.13
AIR ( $\mu\text{U}/\text{ml}$ )*	48.4 ± 3.0	0.005	34.1 ± 4.0	0.22	44.3 ± 8.7	34.5 ± 5.6	38.9 ± 5.0	0.27	31.5 ± 5.1	30.6 ± 4.6
AIR adjusted for $S_1$ ( $\mu\text{U}/\text{ml}$ )*	57.4 ± 3.5	<0.001	38.9 ± 4.1	0.49	44.3 ± 7.7	35.9 ± 5.0	31.2 ± 3.6	0.049	22.0 ± 3.3	17.5 ± 2.6
$\Delta S_1 \times 10^{-4}$ ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$ )*	-0.72 ± 0.09	<0.001	-1.31 ± 0.13	0.38	-1.27 ± 0.16	-0.60 ± 0.19	-0.41 ± 0.11	0.93	-0.33 ± 0.12	-0.09 ± 0.10
$\Delta\text{AIR}$ ( $\mu\text{U}/\text{ml}$ )*	13.3 ± 3.3	0.23	15.4 ± 4.9	0.032	-0.3 ± 7.1	10.5 ± 6.0	11.3 ± 5.3	0.47	4.7 ± 4.9	-5.7 ± 3.2
$\Delta\text{AIR}$ adjusted for $S_1$ ( $\mu\text{U}/\text{ml}$ )*	17.4 ± 3.8	0.94	11.4 ± 4.8	0.012	-7.0 ± 5.8	11.8 ± 6.0	10.2 ± 4.1	0.47	4.1 ± 3.3	-1.7 ± 1.9
<b>Blacks</b>										
<i>n</i>	93	—	19	—	5	—	18	—	16	20
$S_1 \times 10^{-4}$ ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$ )*	2.10 ± 0.16	0.42	1.83 ± 0.30	0.86	1.94 ± 0.65	1.12 ± 0.22	1.03 ± 0.24	0.95	1.01 ± 0.23	0.42 ± 0.15
AIR ( $\mu\text{U}/\text{ml}$ )*	69.4 ± 5.8	0.12	50.4 ± 11	0.88	47.5 ± 21	56.8 ± 12	38.9 ± 8.1	0.66	34.5 ± 7.6	27.4 ± 5.4
AIR adjusted for $S_1$ ( $\mu\text{U}/\text{ml}$ )*	83.1 ± 6.9	0.022	55.1 ± 9.6	0.98	54.6 ± 21	48.9 ± 8.5	32.1 ± 6.0	0.63	28.5 ± 5.6	16.8 ± 3.1
$\Delta S_1 \times 10^{-4}$ ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$ )*	-0.91 ± 0.10	0.75	-0.90 ± 0.20	0.55	-1.18 ± 0.37	-0.06 ± 0.21	-0.14 ± 0.20	0.11	-0.53 ± 0.17	-0.15 ± 0.13
$\Delta\text{AIR}$ ( $\mu\text{U}/\text{ml}$ )*	30.9 ± 6.2	0.092	6.7 ± 8.0	0.24	-9.3 ± 11	48.2 ± 15	1.7 ± 5.9	0.75	-0.7 ± 5.2	-2.4 ± 3.4
$\Delta\text{AIR}$ adjusted for $S_1$ ( $\mu\text{U}/\text{ml}$ )*	33.3 ± 6.9	0.066	4.5 ± 8.1	0.16	-14.6 ± 11	50.1 ± 14	4.2 ± 5.1	0.42	-0.9 ± 4.1	-0.5 ± 2.2
<b>Hispanics</b>										
<i>n</i>	114	—	43	—	18	—	39	—	19	30
$S_1 \times 10^{-4}$ ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$ )*	2.19 ± 0.16	0.034	1.61 ± 0.22	0.58	1.41 ± 0.31	1.10 ± 0.22	1.01 ± 0.17	0.56	0.86 ± 0.22	0.55 ± 0.15
AIR ( $\mu\text{U}/\text{ml}$ )*	68.0 ± 4.9	0.54	62.8 ± 7.3	0.075	43.8 ± 8.1	50.4 ± 8.2	58.6 ± 6.8	0.018	37.0 ± 6.4	23.8 ± 3.3
AIR adjusted for $S_1$ ( $\mu\text{U}/\text{ml}$ )*	80.6 ± 5.0	0.059	64.7 ± 6.8	0.023	42.9 ± 7.0	45.6 ± 6.3	51.4 ± 5.4	0.004	30.6 ± 4.9	17.5 ± 2.2
$\Delta S_1 \times 10^{-4}$ ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$ )*	-0.80 ± 0.10	0.92	-0.64 ± 0.14	0.23	-0.84 ± 0.17	-0.06 ± 0.20	-0.43 ± 0.12	0.81	-0.44 ± 0.15	-0.24 ± 0.11
$\Delta\text{AIR}$ ( $\mu\text{U}/\text{ml}$ )*	23.7 ± 5.0	0.15	10.4 ± 6.6	0.54	2.5 ± 6.6	5.6 ± 7.1	-1.9 ± 5.4	0.55	-4.4 ± 4.5	-2.5 ± 2.3
$\Delta\text{AIR}$ adjusted for $S_1$ ( $\mu\text{U}/\text{ml}$ )*	26.5 ± 5.6	0.15	10.0 ± 6.5	0.30	-0.6 ± 5.8	9.8 ± 6.7	-1.4 ± 4.5	0.49	-3.8 ± 3.6	-1.3 ± 1.7

Data are means ± SE. *P* values are for test of difference in means of the two adjacent categories. \*Log transformed for analysis and back transformed for presentation.

findings in a relatively small high-diabetes risk population ( $n = 17$  Pima Indians who transitioned and  $n = 31$  control subjects), based on clamp studies, are in line with results of the present study, as well as findings in 156 nondiabetic subjects from the U.K., based on an OGTT (15). In this latter study, impaired pancreatic  $\beta$ -cell glucose sensitivity as well as whole-body insulin sensitivity predicted deteriorating glucose tolerance over 5 years. In the UKPDS, deterioration of glycemic control in patients with type 2 diabetes was associated with progressive loss of  $\beta$ -cell function (8). This deterioration of  $\beta$ -cell function occurred without substantial change in insulin sensitivity, as determined by homeostasis model assessment of insulin resistance (16,17). Based on an extrapolation of these findings, it has been suggested that deterioration in  $\beta$ -cell function may commence 10–12 years before diabetes is diagnosed (17).

In the present study, we found that over time mean insulin sensitivity invariably declined but that the change in AIR differed by baseline/follow-up glucose tolerance status. The decline in AIR in relation to deteriorating glucose tolerance status was independent of  $S_i$  at baseline. We also found that subjects whose glucose tolerance status declined over time were those who started with lower  $S_i$  or lower AIR. The decline in  $S_i$  in the IRAS over time may simply reflect the relation of decreasing  $S_i$  to increasing age (18). The magnitude of this decline in the current population within 5.2 years, however, is striking (35% in NGT/NGT). In a previous study,  $S_i$  in elderly men (57–82 years old) was diminished by 63% compared with young men (18–36 years old) (18).

The IRAS has two populations at high risk for the development of type 2 diabetes, namely, Hispanics and African Americans. Previous data from the IRAS (13) indicate that both Hispanics and African Americans are more insulin resistant than non-Hispanic whites, a finding similar to the data on Pima Indians (3). In a few reports (19), nonbese African Americans are said to have a subgroup of insulin-sensitive diabetic subjects. To date no study has examined progression to diabetes in African Americans. Data in this report suggest that there is a marked decrease in insulin secretion associated with the transition to diabetes in all ethnic groups, including African Americans. In addition, the subjects in each ethnic group increased their insulin resistance, although this increase did not differentiate between subjects whose glucose tolerance status did or did not deteriorate.

We would also like to mention potential limitations of the current report. We express insulin secretion as the acute rise in insulin concentration in response to an intravenous glucose load (AIR), reflecting first-phase insulin secretion, at best. Thus, we have no information about second-phase insulin secretion or other more subtle aspects of  $\beta$ -cell function, such as the potentiation of insulin release by glucose or the pulsatility and oscillation of insulin secretion. Furthermore, the use of the FSIGTT to assess insulin sensitivity resulted in subjects whose  $S_i$  calculated by the minimal model was 0. This, however, is unlikely to have affected the current results because 1) previous analyses indicate that subjects with  $S_i = 0$  are correctly classified as being very insulin resistant (20) and 2) only few subjects (particularly in NGT and IGT) presented with  $S_i = 0$ .

In summary, over 5.2 years, mean insulin sensitivity declined in each glucose tolerance category. The change in AIR, however, principally determined glucose tolerance status at follow-up; NGT was maintained by a compensa-

tory increase in insulin secretion. Failure to increase insulin secretion led to IGT, and a decrease in insulin secretion led to overt diabetes. This data may have important implications for the prevention and treatment of type 2 diabetes.

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