β-Cell Dysfunction in Subjects With Impaired Glucose Tolerance and Early Type 2 Diabetes

Comparison of Surrogate Markers With First-Phase Insulin Secretion From an Intravenous Glucose Tolerance Test

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OBJECTIVE—Methods to assess β-cell function in clinical studies are limited. The aim of the current study was to compare a direct measure of insulin secretion with fasting surrogate markers in relation to glucose tolerance status.

RESEARCH DESIGN AND METHODS—In 1,380 individuals from the Insulin Resistance Atherosclerosis Study, β-cell function was assessed using a frequently sampled intravenous glucose tolerance test (first-phase insulin secretion; acute insulin response [AIR]), homeostasis model assessment of β-cell function (HOMA-B), proinsulin levels, and the proinsulin-to-insulin ratio. β-Cell function was cross-sectionally analyzed by glucose tolerance categories (normal glucose tolerance [NGT], $n = 712$; impaired glucose tolerance [IGT], $n = 353$; newly diagnosed diabetes by 2-h glucose from an oral glucose tolerance test [OGTT] [DM2h], $n = 80$; newly diagnosed diabetes by fasting glucose [DMf], $n = 135$; or newly diagnosed diabetes by fasting and 2-h glucose and established diabetes on diet/exercise only [DM], $n = 100$).

RESULTS—In Spearman correlation analyses, proinsulin and the proinsulin-to-insulin ratio were only modestly inversely related to AIR (r values from −0.02 to −0.27), and AIR was strongly related to HOMA-B (r values 0.56 and 0.58). HOMA-B markedly underestimated the magnitude of the β-cell defect across declining glucose tolerance, especially for IGT and new DM by OGTT compared with AIR. Analyses adjusting for insulin sensitivity showed that β-cell function was compromised in IGT, DM2h, DMf, and DM, relative to NGT, by 13, 12, 59, and 62% (HOMA-B) and by as much as 40, 60, 80, and 75%, using AIR.

CONCLUSIONS—Subjects with IGT and early-stage, asymptomatic type 2 diabetic patients have more pronounced β-cell defects than previously estimated from epidemiological studies using homeostasis model assessment. ***Diabetes*** **57:1638–1644, 2008**

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AIR, acute insulin response; DM, newly diagnosed diabetes by both fasting and 2-h hyperglycemia and patients with established type 2 diabetes on diet only; DM2h, newly diagnosed type 2 diabetes based on 2-h oral glucose tolerance test levels; DMf, newly diagnosed type 2 diabetes based on fasting glucose levels; HOMA, homeostasis model assessment; HOMA-B, HOMA of β-cell function; HOMA-IS, HOMA of insulin sensitivity; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; S_I, insulin sensitivity index; UKPDS, UK Prospective Diabetes Study.

Several methods have been developed to assess pancreatic β-cell function; however, all methods have limitations (1). Direct measures, such as the hyperglycemic clamp (2) and the acute insulin response (AIR) from an intravenous glucose tolerance test (3) are laborious and expensive procedures and, therefore, are rarely used in larger-scale clinical research and are irrelevant for clinical practice. Instead, surrogate markers based on fasting blood samples are often used; namely, homeostasis model assessment (HOMA) based on simultaneous measures of fasting glucose and insulin levels (4), proinsulin levels, and the proinsulin-to-insulin ratio (5). Stimulated (such as AIR) and fasting measures (such as HOMA) may not be directly comparable, and it is still a matter of debate as to which particular aspects of β-cell function these measures relate and, ultimately, to what extent these measures truly reflect β-cell function (1,4).

Based on HOMA findings from the UK Prospective Diabetes Study (UKPDS), it has been suggested that in patients with type 2 diabetes, β-cell function is reduced by 50% at the time of diagnosis (6) and, hence, that loss of β-cell function begins 10–12 years before diagnosis (7). The magnitude of β-cell dysfunction in patients at risk of diabetes (impaired glucose tolerance [IGT]) or early type 2 diabetes (as detected by oral glucose tolerance test [OGTT]) has not been studied in a large population using a direct measure of β-cell function.

Therefore, the aim of the current study was to assess β-cell function by comparing a direct measure of insulin secretion, the AIR from an intravenous glucose tolerance test, with surrogate markers of β-cell function across varying states of glucose tolerance (including IGT and early type 2 diabetes) in a large, tri-ethnic population, 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 cardiovascular disease across different ethnic groups and varying states of glucose tolerance. A full description of the design and methods of the IRAS has been published previously (8). The IRAS protocol was approved by local institutional review committees, and all subjects gave informed consent. The 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. Height, weight, and girth measurements and other laboratory measurements were performed using standard methods, as described previously (8).

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

TABLE 1
Baseline characteristics stratified by glucose tolerance status

	NGT	IGT	DM2h	DMf	DM
n	712	353	80	135	100
Age (years)	53.0 (47.0, 61.0)	57.0 (50.0, 64.0)	61.5 (55.5, 66.0)	57.0 (50.0, 64.0)	56.5 (50.0, 64.0)
Female (%)	53.9	62.0	61.3	57.8	51.0
African American (%)	25.6	26.1	25.0	45.9	30.0
Hispanic (%)	33.8	34.8	43.8	19.3	33.0
Non-Hispanic white (%)	40.6	39.1	31.3	34.8	37.0
Waist circumference (cm)	87.9 (79.5, 96.0)	95.1 (86.0, 102.1)	96.3 (88.9, 103.0)	100.0 (92.8, 108.6)	99.4 (90.0, 105.4)
BMI (kg/m^2)	26.7 (24.3, 29.5)	28.9 (26.0, 33.7)	29.6 (26.8, 32.7)	32.2 (28.7, 36.3)	30.4 (26.8, 34.1)
Fasting glucose (mmol/l)	5.2 (4.9, 5.6)	5.8 (5.3, 6.2)	6.3 (5.7, 6.7)	8.0 (7.3, 9.3)	8.3 (7.0, 10.7)
2-h glucose (mmol/l)	5.9 (5.1, 6.8)	8.9 (8.2, 9.9)	12.5 (11.7, 13.8)	14.8 (12.5, 18.0)	15.5 (13.2, 20.5)
Fasting insulin (pmol/l)	72.0 (48.0, 102.0)	90.0 (66.0, 132.0)	126.0 (78.0, 180.0)	129.0 (84.0, 192.0)	120.0 (84.0, 192.0)
HOMA-IS (%)	75.0 (52.4, 110)	57.0 (39.2, 80.3)	40.3 (28.7, 66.1)	37.0 (26.3, 55.4)	36.2 (25.7, 55.8)
S_I ($10^{-4} \times min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	2.01 (1.15, 3.50)	1.05 (0.54, 1.69)	0.42 (0.00, 0.84)	0.39 (0.00, 0.84)	0.37 (0.00, 0.81)
$S_I = 0$ (%)	2.1	12.9	32.9	32.2	33.7
Proinsulin (pmol/l)	4.00 (2.90, 5.90)	6.00 (3.90, 9.80)	8.35 (6.30, 16.0)	14.0 (8.80, 23.0)	13.5 (8.60, 23.0)
Proinsulin-to-insulin ratio	0.06 (0.04, 0.09)	0.07 (0.05, 0.10)	0.08 (0.06, 0.12)	0.10 (0.07, 0.15)	0.10 (0.07, 0.15)
HOMA-B	103 (80.2, 132)	107 (83.0, 135)	117 (83.0, 142)	68.8 (49.7, 96.1)	58.1 (36.5, 104)
AIR (μU/ml)	56.5 (32.0, 91.5)	44.0 (24.5, 75.5)	45.2 34.3 (20.3, 56.3)	19.0 (14.0, 30.0)	21.0 (14.0, 35.5)

Data are medians (Q_1, Q_3) or %.

years), 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 (all comparisons, $P > 0.32$). Longitudinal data as derived from the follow-up examination were used for the sole purpose of defining a normal glucose tolerant (NGT)/NGT population (NGT at baseline and at follow-up) as a reference for assessing the magnitude of β-cell dysfunction across various glucose tolerance categories. Therefore, this report includes cross-sectional data in 1,380 subjects stratified as follows: NGT ($n = 712$), IGT (as defined by World Health Organization criteria; $n = 353$), newly diagnosed type 2 diabetes based on fasting glucose levels (≥126 mg/dl; $n = 135$) (DMf), newly diagnosed type 2 diabetes based on 2-h OGTT glucose levels (≥200 mg/dl; $n = 80$) (DM2h), or newly diagnosed diabetes by both fasting and 2-h hyperglycemia and patients with established type 2 diabetes on diet only ($n = 100$) (DM).

A standard 75-g OGTT was performed. A frequently sampled intravenous glucose tolerance test (9) with minimal model analysis (10) 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 insulin sensitivity index (S_I), 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 (this value correlates with the MINMOD-derived AIR [10]; $r = 0.93$, $P < 0.0001$).

Glucose and insulin levels in all samples were measured at the central IRAS laboratory at the University of Southern California (Los Angeles). Plasma glucose was measured with the glucose oxidase technique on an automated autoanalyzer (Yellow Springs Equipment). Insulin was measured using the dextran-charcoal radioimmunoassay (11). This insulin assay cross-reacts with proinsulin. The split-pair coefficient of variation (CV) for the insulin radioimmunoassay was 19% ($n = 163$). Fasting serum intact proinsulin and split proinsulin were determined from samples stored at −70°C for an average of 3.3 years (35, 44 months) by means of highly specific two-site monoclonal antibody–based immunoradiometric assays (12). The split-pair CVs were 14% for proinsulin ($n = 98$) and 18% for split proinsulin ($n = 98$). There was no detectable cross-reactivity of insulin or split proinsulin in the intact proinsulin assay. Insulin did not significantly cross-react in the assay for split proinsulin, and the cross-reactivity of intact proinsulin in this assay was 84%. Assay values of split proinsulin were corrected for this by subtracting the corresponding proinsulin cross-reactivity. The assay of split proinsulin cross-reacts equally with 32-33, des-32, and des-31-32 split proinsulins. We used the term "split proinsulin" to indicate the sum of these three molecules, the majority of which are des-31-32 split proinsulin (5,13). The sensitivity limit of the intact proinsulin and split proinsulin assays was 1.25 pmol/l (3 SDs from 0). Intact proinsulin and split proinsulin were determined at the laboratory of the Department of Clinical Biochemistry at Addenbrook's Hospital (Cambridge, U.K.) (Prof. C.N. Hales).

Statistical analyses. HOMA insulin secretion and insulin sensitivity measures were calculated using the 1998 computer program (14). ANCOVA and Spearman correlations were calculated using SAS version 9.1. Log-transformed values were used in all analyses for all continuous variables that appeared to be more normally distributed with the transformation than without. It has been suggested that HOMA of β-cell function (HOMA-B) values be interpreted in the context of concomitant insulin resistance (4); therefore, multivariate analyses (adjusting for HOMA of insulin sensitivity [HOMA-IS]) were performed in addition to univariate analyses. All measures of insulin sensitivity and insulin secretion were also log transformed so that models adjusting insulin secretion for insulin sensitivity would conform to the established hyperbolic-shaped relationship within each glucose tolerance category. More detailed analyses of the AIR-S_I relationship across glucose tolerance categories in the IRAS have been published (15).

In the case of S_I, S_I+1 was log transformed because the logarithm of 0, a valid value for S_I, is undefined. For ease of comparison, ANCOVA results are indexed by multiplying the means by 100 divided by the mean for the normal group (either all subjects with NGT at the baseline examination or those who were NGT at both baseline and follow-up). Main effect and interaction terms for ethnicity were added to ANCOVA models to test for significant heterogeneity. P values <0.05 are reported as statistically significant.

RESULTS

Table 1 shows baseline characteristics stratified by glucose tolerance status, including measures of insulin resistance and insulin secretion, respectively. Insulin resistance (as assessed by HOMA-IS and minimal-model S_I) gradually deteriorated with deteriorating glucose tolerance status (from NGT to DM); by contrast, insulin secretion, as assessed by HOMA-B, (slightly) increased in IGT and DM2h versus NGT but decreased in DMf and DM (with no difference between the latter two); insulin secretion as assessed by AIR decreased from NGT to IGT and DM2h and further to DMf and DM (with no difference between the latter two).

To estimate the magnitude of β-cell dysfunction by

TABLE 2
Measures of insulin resistance and insulin secretion stratified by glucose tolerance status at baseline indexed to NGT at baseline

	NGT	*P**	IGT	*P**	DM2h	*P**	DMf	*P**	DM
n	712		353		80		135		100
HOMA-IS	100.0 ± 2.3	<0.0001	73.6 ± 2.5	0.007	59.8 ± 4.3	0.019	48.7 ± 2.7	0.53	51.3 ± 3.3
S_I	100.0 ± 2.7	<0.0001	49.2 ± 2.6	<0.0001	23.2 ± 4.1	0.71	21.3 ± 3.0	0.88	20.7 ± 3.4
Fasting insulin	100.0 ± 2.4	<0.0001	134.3 ± 4.6	0.011	163.6 ± 11.9	0.15	185.9 ± 10.3	0.37	172.7 ± 11.2
Proinsulin	100.0 ± 2.7	<0.0001	148.3 ± 5.8	0.0001	220.5 ± 22.0	0.0004	330.5 ± 21.5	0.82	323.2 ± 26.3
1/Proinsulin	100.0 ± 2.7	<0.0001	67.4 ± 2.6	0.0001	45.3 ± 4.5	0.0004	30.3 ± 2.0	0.82	30.9 ± 2.5
Proinsulin-to-insulin ratio	100.0 ± 2.7	0.015	111.8 ± 4.3	0.082	133.2 ± 13.0	0.019	173.1 ± 11.0	0.74	178.9 ± 14.2
1/Proinsulin-to-insulin ratio	100.0 ± 2.7	0.015	89.4 ± 3.4	0.082	75.1 ± 7.3	0.019	57.8 ± 3.7	0.74	55.9 ± 4.4
Split proinsulin	100.0 ± 3.3	<0.0001	159.6 ± 7.7	<0.0001	274.6 ± 34.1	0.017	383.6 ± 30.9	0.56	356.9 ± 36.0
1/Split proinsulin	100.0 ± 3.3	<0.0001	62.7 ± 3.0	<0.0001	36.4 ± 4.5	0.017	26.1 ± 2.1	0.56	28.0 ± 2.8
Split proinsulin–to–insulin ratio	100.0 ± 2.8	0.0001	120.3 ± 4.9	0.002	165.9 ± 17.0	0.11	199.7 ± 13.4	0.92	197.6 ± 16.5
1/Split proinsulin–to–insulin ratio	100.0 ± 2.8	0.0001	83.1 ± 3.4	0.002	60.3 ± 6.2	0.11	50.1 ± 3.4	0.92	50.6 ± 4.2
HOMA-B	100.0 ± 1.7	0.20	103.8 ± 2.5	0.71	106.0 ± 5.5	<0.0001	63.0 ± 2.5	0.042	55.8 ± 2.6
AIR	100.0 ± 2.9	<0.0001	78.5 ± 3.3	0.045	64.5 ± 6.0	<0.0001	38.3 ± 2.7	0.29	42.6 ± 3.4
Adjusted for insulin sensitivity									
HOMA-B adjusted for HOMA-IS	100.0 ± 1.1	<0.0001	86.7 ± 1.3	0.003	78.3 ± 2.4	<0.0001	41.3 ± 1.0	0.010	37.7 ± 1.1
AIR adjusted for S_I	100.0 ± 2.9	<0.0001	59.7 ± 2.4	<0.0001	39.5 ± 3.5	<0.0001	22.6 ± 1.5	0.21	25.4 ± 1.9

Data are geometric means ± SE. For each measure, the overall *F*-test across the five categories is significant at $P < 0.0001$. **P* value from comparison of adjacent columns.

deteriorating glucose tolerance status, data were indexed to data from subjects with NGT at baseline (Table 2; Fig. 1) and from subjects with NGT both at baseline and at the IRAS follow-up examination (NGT/NGT) (Fig. 2).

Relative to NGT, intact proinsulin, split proinsulin, the proinsulin-to-insulin ratio, and the split proinsulin–to–insulin ratio showed a steady increase with deteriorating glucose tolerance, with no difference between DMf and DM (Table 2). HOMA-B, by contrast, was not different between NGT, IGT, and DM2h and decreased significantly in DMf and DM, with no difference between the latter two. In analyses adjusting for insulin sensitivity, β-cell function was compromised by 13% (HOMA-B) to 40% (AIR) in IGT; in newly diagnosed type 2 diabetes, based on an OGTT (DM2h), from 12% (HOMA-B) up to 60% (AIR) and based on fasting values (DMf) from 59% (HOMA-B) up to 77% (AIR) and in newly diagnosed diabetes with both fasting hyperglycemia and hyperglycemia after challenge or diabetes on diet only (DM), from 62% (HOMA-B) to 75% (AIR). When using IFG/NGT as a separate category ($n = 58$), a 38% reduction in HOMA-B and a 44% reduction in AIR, relative to NFG/NGT (adjusted for insulin resistance, respectively), were found (data not shown).

Proinsulin levels (both intact and split), i.e., 1/proinsulin and 1/split proinsulin, slightly overestimated the β-cell defect (Fig. 1*A*), compared with AIR, in unadjusted analyses but underestimated the defect in analyses adjusting for insulin resistance (Fig. 1*B*); by contrast, HOMA-B underestimated β-cell dysfunction, relative to AIR, particularly in IGT and DM2h, and to a lesser degree in DMf and DM (Fig. 1). Adjustment for insulin resistance decreased this gap between HOMA and AIR to some extent (Fig. 1*B*).

When data were indexed to subjects with NGT at baseline and follow-up (NGT/NGT), similar results were found; however, the magnitude of the β-cell defect relative to the reference group, as well as the gap between AIR and surrogate markers, was generally greater (Fig. 2).

Spearman correlation analyses (Table 3). Proinsulin and the proinsulin-to-insulin ratio were only modestly inversely related to AIR (r values from −0.02 to −0.27), and AIR was strongly related to HOMA-B (r values 0.56 and 0.58) (Table 3).

Heterogeneity analyses (Table 4). The pattern seen in the overall population (Table 2; Figs. 1 and 2) was consistently seen across the three ethnic groups of the IRAS. We detected one *P* value reaching statistical significance for the interaction of ethnicity for HOMA-B ($P < 0.012$), driven by relatively high values of HOMA-B in whites compared with blacks and Hispanics. This finding, however, may have been due to chance given the large number of comparisons made.

DISCUSSION

The present study yielded two major findings: First, β-cell function, as assessed using a direct measure of (first-phase) insulin secretion (AIR) is markedly compromised in IGT and early type 2 diabetes (as newly diagnosed by OGTT). And second, surrogate markers of β-cell function, including HOMA, underestimate the magnitude of the β-cell defect across declining glucose tolerance status, especially for IGT and new DM by OGTT, compared with a direct measure of insulin secretion (AIR). Findings were consistent across the three ethnic groups of the IRAS.

The relationship between glucose and insulin in the basal state (as expressed by HOMA) reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β-cells (16), whereas AIR reflects first-phase insulin secretion—hence, two different aspects of pancreatic β-cell function. Both measures, however, are highly inter-

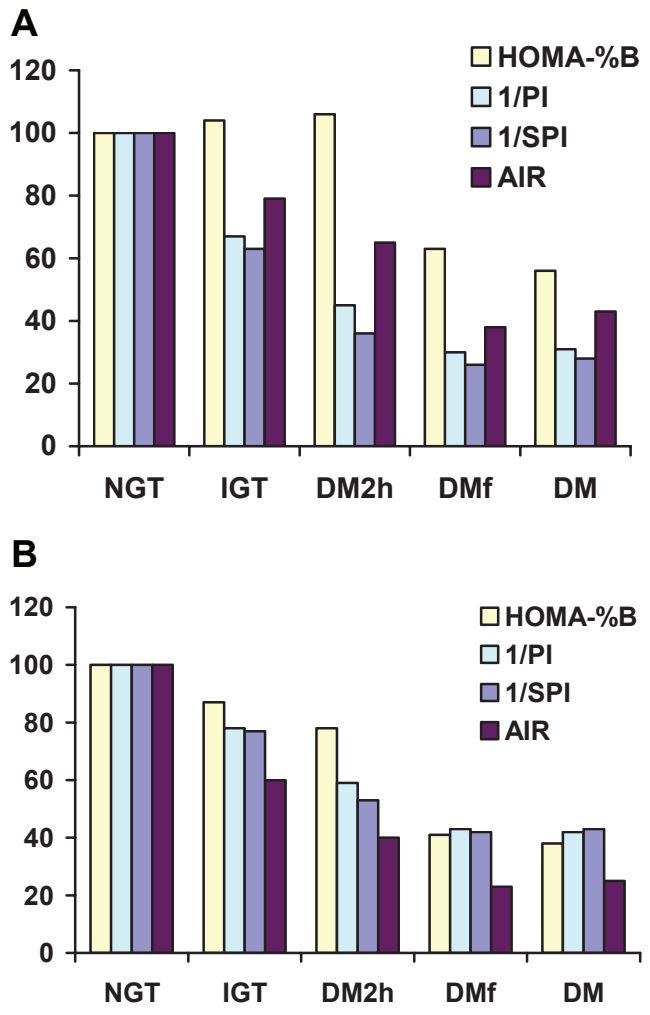

FIG. 1. Measures of β-cell function in all study subjects stratified by glucose tolerance status at baseline indexed to NGT at baseline (NGT). *A*: Unadjusted. *B*: Adjusted for insulin resistance; HOMA-%B for HOMA-IS, 1/proinsulin and 1/split proinsulin for 1/insulin, and AIR for S_I. PI, proinsulin; SPI, split proinsulin.

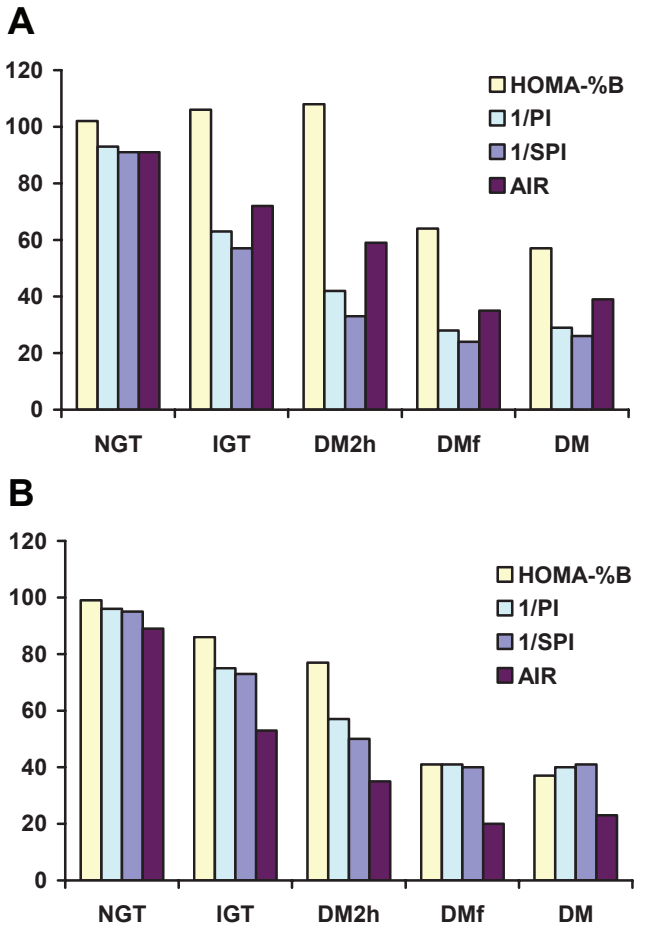

FIG. 2. Measures of β-cell function in all study subjects stratified by glucose tolerance status at baseline indexed to NGT both at baseline and follow-up (NGT/NGT). *A*: Unadjusted. *B*: Adjusted for insulin resistance; HOMA-%B for HOMA-IS, 1/proinsulin and 1/split proinsulin for 1/insulin, and AIR for S_I. PI, proinsulin; SPI, split proinsulin.

related. Of interest, although HOMA-B was strongly related to AIR, based on correlation analyses (Table 3), HOMA-B failed to discriminate between glucose tolerance categories, whereas AIR and also proinsulin levels only modestly related to AIR in correlation analyses, discriminated between categories. Previous reports indicate that AIR and proinsulin levels predict incident type 2 diabetes (17,18) and insulin secretion, as assessed by HOMA (19). Potential limitations of the use of HOMA as a measure of insulin resistance and β-cell function, respectively, have been discussed in detail previously (4,20–22), including its lack of capture of brain glucose uptake; its lack of capture of the stimulated state by relying on fasting measures; its insensitivity to a variable β-cell glycemic sensitivity; its insensitivity to factors affecting insulin secretion other than glucose, such as amino acids fatty acids, cortisol, or growth hormone (22); and considerations around reproducibility of the method (21). These limitations and further research in developing simple markers of insulin resistance/secretion notwithstanding, HOMA is still considered a preferred method in large epidemiological studies (20) and is considered useful in research to discover the pathogenesis of type 2 diabetes (21).

A large study in Pima Indians showed modest correlations of indexes derived from an OGTT to more sophisti-

TABLE 3
Spearman correlation analyses (overall population)

	Proinsulin-to-insulin ratio	HOMA-%B	AIR	AIR adjusted for S_I	S_I
Proinsulin	0.56	0.13	−0.02 (NS)	−0.10*	−0.63
Proinsulin-to-insulin ratio	—	−0.51	−0.26	−0.27	−0.09
HOMA-B	—	—	0.58	0.56	−0.27
AIR	—	—	—	—	−0.09*

All P values <0.0001, except *P < 0.005 and NS.

TABLE 4
Measures of insulin secretion stratified by ethnicity and glucose tolerance status at baseline indexed to NGT at baseline

	Ethnicity	NGT	*P**	IGT	*P**	DM2h	*P**	DMf	*P**	DM	Interaction *P* value
Proinsulin	White	100.0 ± 4.1	<0.0001	136.9 ± 8.4	0.002	222.5 ± 35.3	0.001	396.9 ± 42.4	0.65	368.6 ± 50.2	0.057
	Black	100.0 ± 5.5	<0.0001	155.2 ± 12.4	0.011	270.5 ± 61.2	0.94	265.8 ± 26.8	0.32	315.1 ± 47.6	–
	Hispanic	100.0 ± 4.8	<0.0001	156.4 ± 10.6	0.2	194.0 ± 32.4	0.002	368.5 ± 55.3	0.18	283.2 ± 41.5	–
1/Proinsulin	White	100.0 ± 4.1	<0.0001	73.1 ± 4.5	0.002	44.9 ± 7.1	0.001	25.2 ± 2.7	0.65	27.1 ± 3.7	0.057
	Black	100.0 ± 5.5	<0.0001	64.4 ± 5.2	0.011	37.0 ± 8.4	0.94	37.6 ± 3.8	0.32	31.7 ± 4.8	–
	Hispanic	100.0 ± 4.8	<0.0001	63.9 ± 4.3	0.2	51.5 ± 8.6	0.002	27.1 ± 4.1	0.18	35.3 ± 5.2	–
Proinsulin-to-insulin ratio	White	100.0 ± 4.1	0.14	111.1 ± 6.7	0.1	143.5 ± 22.4	0.47	163.2 ± 17.3	0.51	181.3 ± 24.2	0.66
	Black	100.0 ± 5.7	0.052	121.2 ± 10.2	0.51	141.0 ± 33.7	0.51	164.9 ± 17.5	0.39	192.7 ± 30.7	–
	Hispanic	100.0 ± 4.5	0.39	106.7 ± 6.7	0.45	120.0 ± 18.6	0.003	214.4 ± 29.9	0.17	166.6 ± 22.7	–
1/Proinsulin-to-insulin ratio	White	100.0 ± 4.1	0.14	90.0 ± 5.4	0.1	69.7 ± 10.9	0.47	61.3 ± 6.5	0.51	55.1 ± 7.4	0.66
	Black	100.0 ± 5.7	0.052	82.5 ± 7.0	0.51	70.9 ± 16.9	0.51	60.6 ± 6.4	0.39	51.9 ± 8.3	–
	Hispanic	100.0 ± 4.5	0.39	93.7 ± 5.9	0.45	83.3 ± 12.9	0.003	46.6 ± 6.5	0.17	60.0 ± 8.2	–
HOMA-B	White	100.0 ± 2.7	0.61	102.5 ± 4.1	0.77	105.5 ± 10.1	0.007	77.6 ± 5.4	0.0006	54.7 ± 4.3	0.012
	Black	100.0 ± 3.4	0.38	95.1 ± 4.6	0.86	97.0 ± 10.3	<0.0001	53.1 ± 3.1	0.89	52.4 ± 4.5	–
	Hispanic	100.0 ± 2.8	0.019	111.8 ± 4.4	0.7	108.3 ± 8.1	<0.0001	63.7 ± 5.6	0.55	59.5 ± 4.6	–
AIR	White	100.0 ± 4.4	0.002	78.2 ± 5.2	0.67	73.0 ± 11.5	0.03	49.0 ± 5.7	0.67	45.7 ± 5.7	0.26
	Black	100.0 ± 6.1	0.0008	70.4 ± 6.2	0.31	57.1 ± 11.6	0.005	31.2 ± 3.4	0.2	39.2 ± 6.0	–
	Hispanic	100.0 ± 4.9	0.027	83.4 ± 5.8	0.019	58.8 ± 8.3	0.01	35.6 ± 5.5	0.45	41.1 ± 5.7	–
AIR adjusted for S_I	White	100.0 ± 4.5	<0.0001	59.1 ± 3.6	0.09	45.8 ± 6.8	0.002	27.4 ± 3.1	0.77	26.2 ± 3.1	0.52
	Black	100.0 ± 6.3	<0.0001	55.0 ± 4.6	0.01	33.6 ± 6.4	0.005	19.4 ± 2.1	0.15	24.7 ± 3.7	–
	Hispanic	100.0 ± 4.9	<0.0001	66.1 ± 4.3	0.0004	39.9 ± 5.4	0.003	22.8 ± 3.4	0.36	27.0 ± 3.6	–

Data are geometric means ± SE. **P* value from comparison of adjacent columns.

cated measures of insulin secretion and sensitivity, respectively (23). This and numerous other studies, using various measures of insulin secretion, demonstrated that β-cell dysfunction precedes the clinical manifestation of type 2 diabetes (rev. in 24). Little information is available, however, about the magnitude of this defect. Based on HOMA results from the UKPDS, it has been suggested that at the time of diagnosis, 50% of β-cell function is already lost and that β-cell dysfunction starts some 10–12 years before the diagnosis of type 2 diabetes (6,7).

In the present study, analyses adjusting for insulin sensitivity (1/HOMA-IS or S_I, respectively) showed that β-cell function, relative to subjects with NGT, was compromised in IGT, DM2h, DMf, and DM by 13, 12, 59, and 62% (HOMA-B) but as much as 40, 60, 80, and 75% using AIR. The β-cell defect was even more pronounced when indexed to a population with "true" NGT, i.e., individuals who remained glucose tolerant throughout the 5.2-year follow-up of the IRAS. These findings indicate *1*) that β-cell defects may be more pronounced early in the pathogenesis of diabetes than previously reported; *2*) that defects of first-phase insulin secretion (AIR) are more pronounced compared with defects as characterized by HOMA-B, particularly in populations with hyperglycemia after challenge (IGT and DM2h); and *3*) that AIR might be a better indicator of early β-cell dysfunction than HOMA-B. Furthermore, a decline in β-cell function may start even earlier (>10 years before diagnosis), and/or the decline in β-cell function over time may be steeper than suggested from the UKPDS. However, our findings are not necessarily contradictory to reports from the UKPDS; the present report represents a population earlier in the diabetes continuum (IGT and diabetes identified by an OGTT vs. clinically diagnosed diabetes in the UKPDS), and by indexing β-cell function to a population with NGT, we were able to compare the magnitude of the defect relative to a control group from the same population sample. In our study, the most severe glucose tolerance category (DM) had a β-cell function (by HOMA-B) of 58% (Table 1), which, however, accounted for only 38% when indexed to NGT and adjusted for prevailing insulin resistance (Table 2). Data based on adjusted analyses is more likely to reflect the prevailing pathophysiology because insulin resistance and insulin secretion are tightly interrelated, and, hence, information is limited and may be misleading when considering one aspect without considering the other (1,24). We would like to note, however, that adjusting HOMA-B for HOMA-IS may be problematic, because both measures contain fasting insulin and glucose values only.

In previous reports, proinsulin and/or the proinsulin-to-insulin ratio have been shown to correlate with AIR (5,25), lending support to the hypothesis that these measures may be used as surrogate markers of β-cell dysfunction (26). Disproportionately elevated proinsulin levels (i.e., proinsulin levels after insulin secretion has been taken into account) have been shown to correlate with direct measures of β-cell dysfunction and to predict incident diabetes (19). Because proinsulin levels have also been shown to correlate with increased insulin resistance (5), adjusted analyses (for insulin sensitivity) were also performed in an attempt to focus on proinsulin levels in the context of insulin secretion. In the present study, fasting proinsulin measures displayed a pattern somewhat closer to AIR than HOMA-B, although fasting intact proinsulin and split proinsulin slightly overestimated the defect in unadjusted analyses and underestimated the defect in analyses adjusting for insulin resistance (vs. AIR, respectively). The role of fasting proinsulin levels (or indexes thereof) as a simple means to assess β-cell function for large-scale clinical trials and eventually the therapeutic decision-making process, needs further evaluation. This will also require that universally accepted assays be able to compare proinsulin levels and proinsulin-to-insulin ratios across studies and populations.

The present report has several limitations: *1*) Findings are based on cross-sectional analyses, yielding no evidence on the course of β-cell function over time across the various stages of glucose tolerance. *2*) We used fasting measures and intravenous glucose tolerance tests as measures of β-cell function rather than measures yielding information about second-phase insulin secretion (such as the hyperglycemic clamp) or after-meal dynamics after oral glucose/meal challenges (OGTT or meal tolerance test). Therefore, we would like to acknowledge that we can only discuss β-cell function (and dysfunction) in the context of these two measures (and limitations thereof), which are unable to cover all complexities of β-cell regulation. Finally, *3*) in the IRAS population, some individuals presented with $S_I = 0$ (Table 1); this may be related to the reduced sampling schedule and the insulin dose used in the IRAS. However, subjects with IGT and type 2 diabetes with $S_I = 0$ are significantly more obese and have greater upper-body adiposity than insulin-resistant subjects with an $S_I > 0$ (27). Also, subjects with $S_I = 0$ have increased cardiovascular risk factors compared with subjects with $S_I > 0$. These results suggest that subjects with $S_I = 0$ are very insulin resistant and probably represent an S_I very close to zero rather than a failure of the minimal model.

In summary, subjects with IGT and early-stage, asymptomatic type 2 diabetic patients have more pronounced β-cell defects than previously estimated from epidemiological studies using HOMA.

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