The Homeostasis Model in the San Antonio Heart Study

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OBJECTIVE — Both insulin resistance and decreased insulin secretion have been shown to predict the development of NIDDM. However, methods to assess insulin sensitivity and secretion are complicated and expensive to apply in epidemiological studies. The homeostasis model assessment (HOMA) has been suggested as a method to assess insulin resistance and secretion from the fasting glucose and insulin concentrations. However, this method has not been extensively evaluated, particularly in different ethnic groups.

RESEARCH DESIGN AND METHODS — We applied the HOMA model to cross-sectional analyses of the San Antonio Heart Study (n = 2,465).

RESULTS — HOMA insulin resistance (IR) was very strongly correlated with fasting insulin (r = 0.98) and HOMA β-cell function (β-cell) was moderately correlated with the 30-min increment in insulin concentration over the 30-min increment in glucose concentration ($\Delta I_{30}/\Delta G_{30}$) in an oral glucose tolerance test (OGTT) (r = 0.44). NIDDM was characterized by both high HOMA IR and low HOMA β-cell function. In Mexican-Americans, HOMA IR in NIDDM subjects was 9.5 compared with 2.7 in normal glucose tolerance (NGT) subjects. In contrast, HOMA β-cell function showed only small differences in Mexican-Americans (176 NIDDM; 257 NGT). However, the $\Delta I_{30}/\Delta G_{30}$ (pmol/mmol) showed much larger differences (75 NIDDM; 268 NGT). When modeled separately, impaired glucose tolerance (IGT) was characterized by high HOMA IR and high HOMA β-cell function. However, when analyzed in the same regression model, high HOMA IR and low HOMA β-cell function characterized subjects with IGT. These results were similar in both ethnic groups. Mexican-Americans had increased insulin resistance (as judged by both HOMA IR and fasting insulin) and insulin secretion (by HOMA β-cell and $\Delta I_{30}/\Delta G_{30}$) relative to non-Hispanic whites.

CONCLUSIONS — We conclude that HOMA provides a useful model to assess insulin resistance and β-cell function in epidemiological studies in which only fasting samples are available and that, further, it is critical to take into account the degree of insulin resistance in assessing insulin secretion by the HOMA model.

Subjects with NIDDM are characterized by peripheral insulin resistance, β-cell failure, and increased hepatic glucose production (1). A number of tests have been developed to evaluate insulin resistance in metabolic ward settings, including the hyperinsulinemic euglycemic clamp (2), the insulin suppression test (3), and the frequently sampled intravenous glucose tolerance (FSIGT) with computer modeling (4). These tests, however, are expensive and have limited patient acceptance for use in large-scale population-based studies. Furthermore, with the exception of the FSIGT, from which the acute insulin response (AIR) may be calculated, the tests do not provide an estimate of insulin secretion.

Fasting insulin concentrations have been used as a surrogate for direct measurement of insulin resistance in epidemiological studies and correlate moderately well with insulin resistance as measured by the hyperinsulinemic euglycemic clamp (r = −0.6) in nondiabetic subjects (5–7). Laakso (7) has proposed that fasting insulin provides a good surrogate for insulin resistance across the range of glucose tolerance. The homeostasis model assessment (HOMA) has been proposed to assess insulin resistance and secretion using the fasting glucose and insulin concentrations (8). Although HOMA has been commonly used in clinical studies, it has not been validated in population-based studies. Anderson et al. (9) have compared the HOMA insulin resistance (IR) to the hyperinsulinemic euglycemic clamp. Since HOMA IR is derived from the fasting insulin and the fasting insulin is considered to be a good surrogate for insulin resistance (7), a more critical question follows: How well does HOMA β-cell function compare with measures of insulin secretion in population studies?

A low increment of insulin to glucose >30 min of an oral glucose tolerance test (OGTT) ($\Delta I_{30}/\Delta G_{30}$) has predicted the development of NIDDM in several populations (10–13), including Mexican-Americans (13). The $\Delta I_{30}/\Delta G_{30}$ is correlated with the AIR from the intravenous glucose tolerance test (14). In this report, we evaluate HOMA IR and β-cell index compared with the fasting insulin and $\Delta I_{30}/\Delta G_{30}$ in cross-sectional analyses in Mexican-Americans (a high-risk population for NIDDM [15]) and non-Hispanic whites (a low-risk population for NIDDM) and in NIDDM and nondiabetic subjects.

RESEARCH DESIGN AND METHODS

— The San Antonio Heart Study is a population-based study of diabetes and cardiovascular disease in Mexican-Americans and non-Hispanic whites. From 1979 to 1982 (phase I) and from 1984 to 1988 (phase II), we randomly selected households from low-income (barrio), middle-income (transitional), and high-income (suburban) census tracts in San Antonio (15,16). All men and nonpregnant women aged 25–64 years who

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ANCOVA, analysis of covariance; AIR, acute insulin response; $\Delta I_{30}/\Delta G_{30}$, 30-minute increment in insulin concentration over the 30-minute increment in glucose concentration; HOMA, homeostasis model assessment; IR, insulin resistance; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; FSIGT, frequently sampled intravenous glucose tolerance; WHR, waist-to-hip ratio; CV, coefficient of variation.

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Table 1—*Clinical and metabolic characteristics of subjects by ethnic group*

	Mexican-Americans	Non-Hispanic whites	*P* value
n	1,862	873	
NIDDM	211 (11.3)	30 (3.4)	<0.001
IGT	245 (13.2)	173 (19.8)	<0.001
Age (years)	43.0 ± 0.3 (25–65)	43.8 ± 0.4 (25–65)	0.760
BMI (kg/m²)	28.7 ± 0.1 (15–58)	26.3 ± 0.2 (15–49)	<0.001
WHR	0.883 ± 0.002 (0.63–1.47)	0.880 ± 0.004 (0.50–1.73)	<0.001
Fasting glucose (mmol/l)	5.21 ± 0.04 (3.5–19.6)	4.83 ± 0.03 (3.5–14.3)	<0.001
2-h glucose (mmol/l)	7.07 ± 0.09 (1.4–30.0)	5.69 ± 0.08 (1.5–21.7)	<0.001
Fasting insulin (pmol/l)	92.7 ± 2.2 (0.6–959.4)	67.7 ± 2.5 (0.6–701.7)	<0.001
2-h insulin (pmol/ml)	615.5 ± 15.0 (8–7,894)	397.5 ± 15.4 (2–3,638)	<0.001
HOMA IR	3.83 ± 0.12 (0.02–72.7)	2.56 ± 0.11 (0.02–44.4)	<0.001
HOMA β-cell index	254.1 ± 7.5 (2.5–5,550)	227.2 ± 14.2 (1.5–7,680)	<0.001
$\Delta I_{30}/\Delta G_{30}$ (pmol/mmol)	245.2 ± 14.8 (0.04–18,873)	205.3 ± 20.5 (0.43–11,172)	0.039

Data are *n* (%) or means ± SE (range).

resided in the randomly sampled households were eligible to participate. Only Mexican-Americans were sampled in the barrio, but approximately equal numbers of each ethnic group were studied in the other types of neighborhoods. Mexican-Americans were defined as individuals whose ancestry and cultural traditions derived from Mexican national origin (17). Detailed descriptions of the two study phases (I and II) have been published previously (15,16). This study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All subjects gave informed consent. Since the phase I baseline examination did not include measurements of post–glucose load insulin concentrations, this report is restricted to subjects from the phase II baseline examination.

Blood specimens were obtained after a 12- to 14-h fast for determination of serum insulin and plasma glucose concentrations. Glucose was measured by a glucose oxidase method. We measured serum insulin with a solid-phase radioimmunoassay (Diagnostic Products, Los Angeles, CA) (18) that shows a high degree of cross-reactivity with proinsulin (~70–100%) (18). The intra-assay coefficient of variation was 6.0% and the interassay coefficient of variation was 8.5%. The lower limit of detectability of the insulin assay is 7 pmol/l. A 75-g oral glucose equivalent load (Koladex or Orangedex, Custom Laboratories, Baltimore, MD) was administered, and blood specimens were obtained 30 min, 1 h, and 2 h later for plasma glucose and serum insulin concentrations. Diabetes and impaired glucose tolerance (IGT) were diagnosed according to World Health Organization (WHO) criteria (19).

Anthropometric measurements (height, weight, and waist and hip circumferences) were made after participants had removed their shoes and upper garments and donned an examining gown (20). Waist circumference was measured at the level of the umbilicus and hip circumference at the level of the greater trochanters. The waist-to-hip ratio (WHR) was used as a measure of upper-body adiposity.

The formulas for the HOMA model (8) are as follows:

$$\text{Insulin resistance (HOMA IR)} = \frac{\text{Fasting insulin (μU/ml)} \times \text{Fasting glucose (mmol/l)}}{22.5}$$

$$\text{β-cell function (HOMA β-cell)} = \frac{20 \times \text{Fasting insulin (μU/ml)}}{\text{Fasting glucose (mmol/l)} - 3.5}$$

If subjects had a fasting glucose of 3.5 mmol/l or greater, they were excluded from the analyses (2.4% of all subjects) to exclude undefined or negative HOMA β-cell function.

Statistical analyses included *t* tests (Table 1), χ^2 tests (Table 1), Spearman's correlations (Table 2), analyses of covariance (ANCOVA) (Table 3), and multiple logistic regression analyses (Tables 4 and 5). The dependent variables in multiple logistic regression were prevalence of NIDDM (Table 4) or IGT (Table 5). Fasting insulin, insulin resistance (HOMA IR), $\Delta I_{30}/\Delta G_{30}$, and HOMA β-cell index were log-transformed to improve skewness and kurtosis. Since fasting insulin and HOMA IR were very highly correlated ($r = 0.976$, $P < 0.001$, overall population) (Table 2), we did not fit these variables in the same regression model. We tested for the presence of ethnic × HOMA IR and ethnic × HOMA β-cell interactions in multiple logistic regression analyses; these interactions were not statistically significant ($P > 0.20$) and thus the effects of HOMA β-cell and IR are similar in each ethnic group. Since the level of insulin secretion may depend on the level of insulin resistance (21,22), we fit HOMA β-cell function and HOMA IR both separately and simultaneously in the same multiple logistic regression model and ANCOVA.

RESULTS — Table 1 shows the clinical and metabolic characteristics of subjects by ethnic group. Mexican-Americans had a higher prevalence of NIDDM, were more obese, and had higher insulin and glucose concentrations. They also had higher HOMA IR, β-cell function, and $\Delta I_{30}/\Delta G_{30}$ than non-Hispanic whites.

Table 2 shows Spearman's correlations between metabolic variables in the overall population and in selected subgroups. All correlations were highly statistically significant ($P < 0.001$), except for $\Delta I_{30}/\Delta G_{30}$ with HOMA IR in the diabetic subset. HOMA IR and fasting insulin were very highly correlated in the overall population ($r = 0.976$) and in all subgroups. The correlation between $\Delta I_{30}/\Delta G_{30}$ and HOMA β-cell was 0.44 in the overall population, 0.38 in nondiabetic subjects, and 0.64 in diabetic subjects. The markers of insulin secretion (HOMA β-cell and $\Delta I_{30}/\Delta G_{30}$) were positively correlated with markers of

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insulin resistance (HOMA IR and fasting insulin) in these univariate analyses.

Table 3 shows metabolic variables by ethnic group and glucose tolerance category. Fasting insulin and HOMA IR increased with worsening glucose tolerance, while $\Delta I_{30}/\Delta G_{30}$ and HOMA β-cell declined in subjects with NIDDM. However, HOMA β-cell was slightly higher in IGT than in normal glucose tolerance (NGT) subjects. The decline in $\Delta I_{30}/\Delta G_{30}$ with worsening glucose tolerance was more striking than for HOMA β-cell. Only after adjustment for HOMA IR was HOMA β-cell lower in IGT than in NGT. Mexican-Americans were significantly more insulin resistant and had higher insulin secretion than non-Hispanic whites at all levels of glucose tolerance.

Table 4 shows the results of multiple logistic regression analyses with the presence of NIDDM as a dependent variable. The results in the overall population, Mexican-Americans, and non-Hispanic whites, were generally similar. Subjects with NIDDM had significantly higher HOMA IR and fasting insulin and lower HOMA β-cell and $\Delta I_{30}/\Delta G_{30}$ than nondiabetic subjects. Note that odds ratio for HOMA β-cell decreased (i.e., became stronger) after further adjustment HOMA IR (models 3–4).

Table 5 shows the results of a multiple logistic regression model in nondiabetic sub-

Table 2—*Spearman correlations between metabolic variables*

	HOMA IR	HOMA β-cell	Fasting insulin	$\Delta I_{30}/\Delta G_{30}$	BMI
Overall population (n = 2,465)					
HOMA IR	—	0.572	0.976	0.151	0.554
HOMA β-cell		—	0.709	0.435	0.316
Fasting insulin			—	0.239	0.546
$\Delta I_{30}/\Delta G_{30}$				—	0.140
Mexican-Americans (n = 1,686)					
HOMA IR	—	0.532	0.968	0.096	0.549
HOMA β-cell		—	0.695	0.458	0.316
Fasting insulin			—	0.210	0.546
$\Delta I_{30}/\Delta G_{30}$				—	0.109
Non-Hispanic whites (n = 779)					
HOMA IR	—	0.652	0.989	0.227	0.485
HOMA β-cell		—	0.745	0.353	0.278
Fasting Insulin			—	0.265	0.473
$\Delta I_{30}/\Delta G_{30}$				—	0.156
Diabetic subjects (n = 223)					
HOMA IR	—	0.393	0.908	0.078*	0.369
HOMA β-cell		—	0.715	0.636	0.351
Fasting insulin			—	0.333	0.434
$\Delta I_{30}/\Delta G_{30}$				—	0.251
Nondiabetic subjects (n = 2,242)					
HOMA IR	—	0.704	0.991	0.311	0.541
HOMA β-cell		—	0.788	0.384	0.362
Fasting insulin			—	0.343	0.532
$\Delta I_{30}/\Delta G_{30}$				—	0.223

*P values not <0.001.

Table 3—*HOMA insulin resistance and HOMA β-cell function and fasting insulin by glucose tolerance status and ethnicity, adjusted for age and sex*

	NGT	IGT	NIDDM	Ethnic	GTT
n					
Mexican-Americans	1,273	218	195		
Non-Hispanic whites	683	68	28		
Fasting insulin (pmol/l)					
Mexican-Americans	77.2 ± 2.3 (100)	129.7 ± 5.5 (168)	153.3 ± 5.9 (190)	<0.001	<0.001
Non-Hispanic whites	60.3 ± 3.1 (100)	106.1 ± 9.9 (176)	151.0 ± 15.4 (250)		
HOMA IR					
Mexican-Americans	2.7 ± 0.1 (100)	5.2 ± 0.3 (193)	9.5 ± 0.3 (352)	<0.001	<0.001
Non-Hispanic whites	2.1 ± 0.2 (100)	4.3 ± 0.5 (204)	8.3 ± 0.7 (396)		
HOMA β-cell function					
Mexican-Americans	257.4 ± 9.6 (100)	298.3 ± 23.1 (116)	175.7 ± 24.7 (68)	0.023	<0.001
Non-Hispanic whites	229.1 ± 12.9 (100)	239.7 ± 41.2 (105)	203.3 ± 64.2 (89)		
$\Delta I_{30}/\Delta G_{30}$ (pmol/mmol/l)					
Mexican-Americans	267.7 ± 16.8 (100)	252.4 ± 40.6 (94)	75.4 ± 43.4 (28)	0.030	<0.001
Non-Hispanic whites	219.1 ± 22.7 (100)	156.4 ± 72.5 (71)	89.5 ± 113.2 (45)		
HOMA β-cell*					
Mexican-Americans	275.6 ± 9.2 (100)	252.6 ± 22.1 (92)	16.5 ± 25.5 (42)	0.017	<0.001
Non-Hispanic whites	262.9 ± 12.5 (100)	216.4 ± 39.2 (82)	73.5 ± 61.7 (66)		

Data are means ± SE (% of NGT) or P values. *Adjusted also for HOMA IR.

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Table 4—*Multiple logistic regression analyses with glucose tolerance (NIDDM vs. nondiabetic) as a dependent variable*

Model	Independent variable	β	SE(β)	χ^2	OR	95% CI
Entire population (n = 2,465)						
1	ln fasting insulin	0.956	0.104	85	2.60	2.12–3.19
2	HOMA IR	0.216	0.017	159	1.24	1.20–1.28
3	HOMA β-cell	−0.002	0.005	17	0.998	0.997–0.999
4	HOMA IR	0.492	0.035	193	1.64	1.53–1.75
	HOMA β-cell	−0.011	0.001	113	0.99	0.987–0.991
5	ln $\Delta I_{30}/\Delta G_{30}$	−1.685	0.108	246	0.19	0.15–0.23
6	ln $\Delta I_{30}/\Delta G_{30}$	−2.178	0.139	246	0.11	0.09–0.15
	ln fasting insulin	1.807	0.151	144	6.09	4.53–8.18
Mexican-Americans (n = 1,686)						
1	ln fasting insulin	0.932	0.112	70	2.54	2.04–3.16
2	HOMA IR	0.215	0.019	134	1.24	1.19–1.29
3	HOMA β-cell	−0.003	0.006	18	0.997	0.996–0.999
4	HOMA IR	0.472	0.038	155	1.60	1.49–1.73
	ln β-cell	−0.011	0.001	96	0.989	0.987–0.991
5	ln $\Delta I_{30}/\Delta G_{30}$	−1.742	0.121	2080	0.18	0.14–0.22
6	ln $\Delta I_{30}/\Delta G_{30}$	−2.182	0.152	206	0.11	0.08–0.15
	ln fasting insulin	1.778	0.166	115	5.92	4.28–8.19
Non-Hispanic whites (n = 779)						
1	ln fasting insulin	1.044	0.277	14	2.84	1.65–4.89
2	HOMA IR	0.217	0.046	23	1.24	1.14–1.36
3	HOMA β-cell	−0.001	0.001	0.50*	0.999	0.997–1.002
4	HOMA IR	0.614	0.107	33	1.85	1.50–2.28
	HOMA β-cell	−0.015	0.003	20	0.985	0.978–0.992
5	ln $\Delta I_{30}/\Delta G_{30}$	−1.621	0.282	33	0.20	0.11–0.34
6	ln $\Delta I_{30}/\Delta G_{30}$	−2.107	0.358	35	0.122	0.06–0.25
	ln fasting insulin	1.781	0.369	23	5.937	2.8–12.3

β, regression coefficient; SE(β), standard error of regression coefficient; OR, odds ratio. Entire population adjusted for age, sex, and ethnicity; Mexican-Americans and non-Hispanic whites adjusted for age and sex. *P = 0.480.

jects with the presence of IGT as the dependent variable. IGT is associated with higher HOMA IR and fasting insulin. Note that high HOMA β-cell predicts IGT (although not significantly) when HOMA β-cell is modeled alone (model 3); however, when HOMA IR is also included in the same regression model, low β-cell predicts IGT (model 4). Low $\Delta I_{30}/\Delta G_{30}$ is significantly related to IGT in Mexican-Americans and to the overall population when modeled alone (model 5); after further adjustment for fasting insulin, low $\Delta I_{30}/\Delta G_{30}$ predicts IGT in all groups. These observations point out the importance of considering insulin resistance in evaluating insulin secretion. The analyses in this table (as in Table 4) were very similar after further adjustment for BMI, WHR, and fasting glucose (data not shown).

CONCLUSIONS — Previous studies have established that subjects with NIDDM have increased insulin resistance and decreased insulin secretion (1–3). In this report, we have shown that using the HOMA model, which uses only the fasting glucose and insulin, increased HOMA IR and decreased HOMA β-cell function are also characteristic of NIDDM. The results were similar in both Mexican-Americans (a high-risk population for NIDDM) and non-Hispanic whites (a low-risk population for NIDDM). That HOMA IR behaves very similarly to fasting insulin is not surprising, given the very strong correlation between these variables. HOMA IR has also been correlated strongly with insulin resistance as determined by the hyperinsulinemic euglycemic clamp (8,9), which is again not surprising, since fasting insulin is highly correlated with hyperinsulinemic euglycemic clamp (5–7). IGT (Table 5) is also associated with higher fasting insulin and HOMA IR.

HOMA β-cell index behaves similarly to the early insulin increment on an oral glucose tolerance suggesting that for evaluating diabetic versus nondiabetic status, information on insulin secretion can be obtained from fasting blood samples. However, potential problems arose with the use of HOMA β-cell predicting IGT status; only after HOMA IR was included in the same regression model did the low HOMA β-cell function characterize IGT. Thus, incorrect results can occur when the HOMA β-cell is used to characterize IGT if the HOMA model is used improperly. According to the HOMA model, subjects with IGT have increased insulin secretion although this relation is not significant. However, adjustment for insulin resistance brings out a latent defect in insulin secretion in subjects with IGT. (In contrast, low $\Delta I_{30}/\Delta G_{30}$ did significantly predict IGT when modeled alone in the overall population and in Mexican-Americans; Table 5, model 5). Bergman et al. (21) described the relationship between insulin sensitivity and resistance from the frequently sampled intravenous glucose tolerance (FSIGT) test, which was further validated in a larger number of subjects (22). Our observations also point out the importance of controlling for insulin resistance when evaluating insulin secretion, as has been previously pointed out (21,22). In a previous cross-sectional study (23), the magnitude of the latent β-cell defect in IGT became much larger when the degree of insulin resistance was taken into account.

We have recently evaluated the use of the HOMA model to predict the development of NIDDM in the Mexico City Diabetes Study (24). Mexicans are genetically similar to Mexican-Americans (25). In that report, HOMA IR, but not HOMA β-cell, predicted NIDDM when both variables were modeled separately. However, when both variables were modeled in the same regression model, both increased HOMA IR, and decreased HOMA β-cell significantly predicted NIDDM. These results are similar to the cross-sectional results for IGT in the current report.

In the original report on the HOMA model (8), HOMA IR was highly correlated with insulin resistance as measured by euglycemic clamp (r = 0.88), and HOMA β-cell was highly correlated with insulin secretion as measured by the hyperglycemic clamp (r = 0.61) and by intravenous glucose tolerance (r = 0.64). However, the precision of the HOMA

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parameters (HOMA β-cell coefficient of variation [CV] = 32%; HOMA IR CV = 31%) was low, making it difficult to develop precise estimates for individual subjects. The HOMA model was developed on a small group of diabetic and nondiabetic subjects. While the results in Tables 4 and 5 suggest a slightly higher χ^2 for HOMA IR than the simple measures for fasting insulin, the HOMA estimates should be considered as a relative rather than an absolute value for insulin resistance.

HOMA IR was reported to be 1.0 in young healthy subjects in the original formulation of the HOMA model (8). In this report, the HOMA was 2.7 in Mexican-Americans and 2.1 in non-Hispanic whites with NGT (Table 3). The population studied in this report was middle-aged and fairly obese (BMI [kg/m^2]: 28.7 Mexican-Americans and 26.3 non-Hispanic whites). Previously, Mexican-Americans were reported to be hyperinsulinemic (18) and insulin resistant (26), relative to non-Hispanic whites.

The current report has a number of strengths including the large number of subjects and a multi-ethnic population. This study also has several limitations. We were not able to compare HOMA IR to more sophisticated measures of insulin resistance, such as the hyperinsulinemic euglycemic clamp secretion or the FSIGT. Moreover, insulin resistance and secretion are complex and dynamic processes, which "baseline" surrogates can only approximate. However, several studies have explored correlations of HOMA IR with hyperinsulinemic euglycemic clamp (8,9). Previous data have also suggested that fasting insulin is a good surrogate for insulin resistance (5–7). Since HOMA IR and fasting insulin are highly correlated, further separate validation of HOMA IR is probably unnecessary. (Since fasting insulin is a determinant of HOMA insulin resistance, the magnitude of the correlation coefficient may, however, be overestimated.) A more important issue is whether HOMA β-cell is a good measure of insulin secretion. In this report, we have compared HOMA β-cell to the ratio of change in insulin to change in glucose over the first 30 min of an OGTT ($\Delta I_{30}/\Delta G_{30}$), which is a direct measure of insulin secretion, since unlike HOMA β-cell, it incorporates stimulated insulin levels. The decline in insulin secretion with worsening glucose tolerance is more marked when assessed by $\Delta I_{30}/\Delta G_{30}$ than by HOMA β-cell (Table 3), suggesting that $\Delta I_{30}/\Delta G_{30}$ may be a superior measure of insulin secretion. However, the $\Delta I_{30}/\Delta G_{30}$ requires a glucose challenge and an additional blood draw. Also, $\Delta I_{30}/\Delta G_{30}$ has recently been shown to be a good predictor of NIDDM in Mexican-Americans (13) and other populations (10–12). In each of the groups in the current report, $\Delta I_{30}/\Delta G_{30}$ was correlated more strongly with HOMA β-cell than with fasting insulin compatible with the concept that HOMA β-cell may be a surrogate for insulin secretion. Another limitation is that we measured insulin using an immunoreactive insulin assay that recognizes proinsulin. Proinsulin is disproportionately elevated in NIDDM (18,27,28) and perhaps in impaired glucose tolerance as well (18,28). However, the ratio of fasting proinsulin/specific insulin in San Antonio Mexican-Americans with IGT (18) is only slightly higher than in subjects with NGT (0.09 vs. 0.07, respectively), and is still relatively low (18). Proinsulin is thus unlikely to confound our measurement of insulin in nondiabetic subjects. Also, a small proportion of subjects (2.4%) had to be excluded since their fasting glucose was <3.5 mmol/l. Watanabe et al. (29) have also shown that the relationship between fasting plasma insulin and insulin sensitivity is not linear. Finally, Rudenski et al. (30) have described a more complex version that also recognizes the effect of glucose resistance or effectiveness. However, we cannot directly evaluate these additional refinements since we only have information on insulin secretion and resistance.

In conclusion, using the HOMA assessment, we have shown that both increased insulin resistance and decreased β-cell function are associated with NIDDM. When modeled independently, both high insulin resistance and secretion are associated with IGT; however, when modeled in the same regression model, high insulin resistance and low insulin secretion are characteristic of IGT. These

Table 5—*Multiple logistic regression analyses in non diabetic subjects with glucose intolerance (IGT vs. NGT) as a dependent variable*

Model	Independent variable	β	SE(β)	χ^2	OR	95% CI
Overall population (n = 2,242)						
1	ln fasting insulin	0.893	0.095	89	2.44	2.03–2.94
2	HOMA IR	0.196	0.021	92	1.22	1.17–1.27
3	HOMA β-cell	0.003	0.002	2*	1.00	0.99–1.01
4	HOMA IR	0.250	0.027	98	1.28	1.27–1.35
	HOMA β-cell	−0.001	0.004	10	0.998	0.997–0.999
5	ln $\Delta I_{30}/\Delta G_{30}$	−0.408	0.082	25	0.67	0.57–0.78
6	ln $\Delta I_{30}/\Delta G_{30}$	−0.871	0.101	75	0.42	0.34–0.51
	ln fasting insulin	1.229	0.107	133	3.42	2.77–4.21
Mexican-Americans (n = 1,491)						
1	ln fasting insulin	0.900	0.114	65	2.46	1.98–3.06
2	HOMA IR	0.191	0.024	68	1.21	1.16–1.27
3	HOMA β-cell	0.003	0.002	2†	1.00	0.99–1.01
4	HOMA IR	0.236	0.030	72	1.27	1.19–1.34
	HOMA β-cell	−0.001	0.004	6‡	0.998	0.997–0.999
5	ln $\Delta I_{30}/\Delta G_{30}$	−0.448	0.094	22	0.64	0.53–0.77
6	ln $\Delta I_{30}/\Delta G_{30}$	−0.897	0.115	60	0.41	0.32–0.51
	ln fasting insulin	1.244	0.125	99	3.47	2.72–4.43
Non-Hispanic whites (n = 751)						
1	ln fasting insulin	0.883	0.185	23	2.42	1.68–3.48
2	HOMA IR	0.216	0.434	28	1.24	1.14–1.35
3	HOMA β-cell	0.001	0.003	0.1¶	1.00	0.999–1.001
4	HOMA IR	0.297	0.061	32	1.35	1.19–1.52
	HOMA β-cell	−0.002	0.001	4§	0.998	0.996–1.000
5	ln $\Delta I_{30}/\Delta G_{30}$	−0.316	0.175	9	0.74	0.52–0.87
6	ln $\Delta I_{30}/\Delta G_{30}$	−0.805	0.210	15	0.45	0.30–0.68
	ln fasting insulin	1.19	0.210	32	3.29	2.18–4.98

Overall population adjusted for age, sex, and ethnicity; Mexican-Americans and non-Hispanic whites adjusted for age and sex. *P = 0.14; †P = 0.11; ‡P = 0.013; §P = 0.047; ¶P = 0.872.

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results are similar in both high- and low-risk populations for NIDDM. Our data suggest that the HOMA model may be a useful method to assess insulin secretion in population-based studies in which only fasting samples are available; however, where an OGTT (with 30-min samples) is available, the latter method is preferable to assess insulin secretion.

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References

1. DeFronzo RA: Lilly Lecture 1987: The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–687, 1988
2. DeFronzo RA, Tobin JD, Andres R: Glucose clamp techniques: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–E223, 1979
3. Shen DC, Shieh SM, Fuh MMT, Wu DA, Chen YDI, Reaven GM: Resistance to insulin stimulated glucose uptake in patients with hypertension. *J Clin Endocrinol Metab* 66:580–583, 1988
4. Bergman RN, Iden YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 236:E667–E677, 1979
5. Hollenbeck CB, Chen N, Chen YDI, Reaven GM: Relationship between the plasma insulin response to oral glucose and insulin stimulated glucose utilization in normal subjects. *Diabetes* 33:460–463, 1984
6. Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YDI, Sands RE, Pei D, Savage PJ, Bergman RN, the Insulin Resistance Atherosclerosis Study Group: A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. *Diabetes* 43:1114–1121, 1994
7. Laakso M: How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 137:959–965, 1993
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RL: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
9. Anderson RL, Hamman RF, Savage PJ, Saad MF, Laws A, Kades WW, Sands RE, Cefalu W for the Insulin Resistance Atherosclerosis Study: Exploration of simple insulin sensitivity measures derived from frequently sampled intravenous glucose tolerance (FSIGT) tests: the Insulin Resistance Atherosclerosis Study. *Am J Epidemiol* 142:724–732, 1995
10. Kosaka K, Hagura R, Kuzuya T: Insulin responses in equivocal and definite diabetes with special reference to subjects who had mild glucose intolerance but later developed definite diabetes. *Diabetes* 26:944–952, 1977
11. Efendic S, Luft R, Wajngot A: Aspects of the pathogenesis of type 2 diabetes. *Endocr Rev* 5:395–410, 1984
12. Kadowaki T, Miyake Y, Hagura R, Akanuma Y, Kajinuma H, Kuzuya N, Takaku F, Kosaka K: Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 26:44–49, 1984
13. Haffner SM, Miettinen H, Gaskill SP, Stern MP: Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican-Americans. *Diabetes* 44:1386–1391, 1995
14. Philips DIW, Clark PM, Hales CN, Osmond C: Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and secretion. *Diabet Med* 11:286–292, 1993
15. Stern MP, Rosenthal M, Haffner SM, Hazuda HP, Franco LJ: Sex difference in the effects of sociocultural status on diabetes and cardiovascular risk factors in Mexican Americans: the San Antonio Heart Study. *Am J Epidemiol* 120:834–851, 1984
16. Haffner SM, Stern MP, Hazuda HP, Pugh JA, Patterson JK: Hyperinsulinemia in a population at high risk for non-insulin dependent diabetes mellitus. *N Engl J Med* 315:220–224, 1986
17. Hazuda HP, Comeaux PJ, Stern MP, Haffner SM, Eifler CW, Rosenthal M: A comparison of three indicators for identifying Mexican Americans in epidemiologic research: methodological findings from the San Antonio Heart Study. *Am J Epidemiol* 123:96–112, 1986
18. Haffner SM, Bowsher RR, Mykkänen L, Hazuda HP, Mitchell BD, Valdez RA, Gingerich R, Monterossa A, Stern MP: Proinsulin and specific insulin concentrations in high- and low-risk populations for NIDDM. *Diabetes* 43:1490–1493, 1994
19. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985, p. 94–98 (Tech. Rep. Ser., no. 727)
20. Haffner SM, Stern MP, Hazuda HP, Pugh JA, Patterson JK, Malina R: Upper body and centralized adiposity in Mexican Americans and non-Hispanic whites: relationship to body mass index and other behavioral and demographic variables. *Int J Obes* 10:493–502, 1986
21. Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in men: measurement of insulin sensitivity and β-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest* 68:1456–1467, 1981
22. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
23. Watanabe RM, Laws A, Rewers M, Bergman RN for the IRAS investigators: Impaired glucose tolerant subjects exhibit a β-cell defect despite normal fasting glycemia (Abstract). *Diabetes* 44 (Suppl. 1):5A, 1995
24. Haffner SM, Gonzalez C, Miettinen H, Kennedy E, Stern MP: A prospective analyses of the HOMA model: the Mexico City Diabetes Study. *Diabetes Care* 19:1138–1141, 1996
25. Stern MP, Gonzalez C, Mitchell BD, Villalpando E, Haffner SM, Hazuda HP: Genetic and environmental determinants of type II diabetes in Mexico City and San Antonio. *Diabetes* 41:484–492, 1992
26. Haffner SM, D'Agostino R, Saad MF, Rewers M, Mykkänen L, Selby J, Howard G, Savage PJ, Hamman RF, Wagenkneckt LE, Bergman RN: Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. *Diabetes* 45:742–748, 1996
27. Temple RC, Clark P, Nagi DK, Schneider A, Yudkin JS, Hales CN: Radioimmunoassay may overestimate insulin in non-insulin dependent diabetics. *Clin Endocrinol (Oxf)* 32:689–693, 1990
28. Davies M, Rayman G, Gray IP, Day JL, Hales CN: Insulin deficiency and increased plasma concentrations of intact and 32/33 split proinsulin in subjects with impaired glucose tolerance. *Diabet Med* 10:313–320, 1993
29. Watanabe R, Bergman R, Sands R, Anderson R: Non-linear relationship between fasting plasma insulin and insulin sensitivity (Abstract). *Clin Res* 42:88A, 1994
30. Rudenski AS, Mathews DR, Levy JC, Turner RC: Understanding "insulin resistance": both glucose resistance and insulin resistance are required to model human diabetes. *Metabolism* 40:908–917, 1991

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