A Prospective Analysis of the HOMA Model

The Mexico City Diabetes Study

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OBJECTIVE — Both insulin resistance (IR) 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 IR and secretion from the fasting glucose and insulin concentrations.

RESEARCH DESIGN AND METHODS — We applied the HOMA model in the 3.5-year follow-up of the Mexico City Diabetes Study.

RESULTS — Out of 1,449 subjects, 97 developed diabetes. When modeled separately, insulin resistance but not insulin secretion predicted NIDDM. However, when both variables were entered into the same regression model, both increased IR and decreased β-cell function significantly predicted NIDDM.

CONCLUSIONS — We conclude that the HOMA provides a useful model to assess β-cell function in epidemiological studies and that it is important to take into account the degree of IR in assessing insulin secretion.

Both insulin resistance (IR) and decreased insulin secretion have been shown to be antecedents of NIDDM. Previous prospective studies have consistently shown that IR (1,2) and hyperinsulinemia (3–7) are strong predictors of NIDDM. Several studies have also suggested that abnormal insulin secretion as assessed either by a low acute insulin response to intravenous glucose, a low increment of insulin relative to glucose 30 min after an oral glucose load, or a low 2-h insulin after a glucose load (1,3,6–9) predict the development of diabetes, especially in subjects with impaired glucose tolerance. Definitive methods to assess insulin sensitivity and secretion are complicated, expensive, and difficult to apply in epidemiological studies. The homeostasis model assessment (HOMA) has been proposed as a method to assess IR and secretion using the fasting glucose and insulin concentrations (10). Yet, few data are available on the ability of insulin secretion and resistance as assessed by the HOMA to predict the development of NIDDM.

In this report, we examine obesity, body fat distribution, glucose tolerance, insulin secretion, and resistance as predictors of NIDDM in the 3.5-year follow-up of Mexico City Diabetes Study, a population-based study of diabetes and cardiovascular risk factors (11).

RESEARCH DESIGN AND METHODS

— In Mexico City, six low-income neighborhoods (colonias) were selected for the study (11). The baseline survey was carried out from February 1990 to October 1992, and 3,326 eligible individuals (35- to 64-year-old men and nonpregnant women) were identified for the study. Of these, 2,813 (84.5%) completed a home interview, and 2,278 completed a medical examination at a clinic (response rate to clinic examination among those who had home interviews, 81.0%; overall response rate, 68.5%). Subjects who attended the clinic examination were similar to those who attended only the home interview in terms of age, sex, and self-reported history of myocardial infarction, diabetes, and smoking. BMI was computed. The waist-to-hip ratio (WHR) circumference was used as a measure of upper body fat distribution.

Blood specimens were obtained after a 12- to 14-h fast, and a second specimen was obtained 2 h after administration of a 75 g glucose load. All laboratory procedures were performed in the Division of Clinical Epidemiology Laboratory in San Antonio. Samples were stored at −70°C until shipped to San Antonio on dry ice. Insulin was measured with a commercial radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA) (12), which has a high degree of cross-reactivity with proinsulin (70–100%). Diabetes (fasting plasma glucose >140 mg/dl and/or a 2-h glucose of >200 mg/dl) and impaired glucose tolerance (fasting plasma glucose <140 mg/dl and 2-h glucose ≥140 mg/dl and <200 mg/dl) were diagnosed according to the criteria of the World Health Organization. Subjects who did not meet these criteria but who reported treatment with oral antidiabetic agents or insulin were also considered to have diabetes. Since this report is concerned with the metabolic precursors of NIDDM, subjects with diabetes at baseline are excluded. In April 1993, we began a 3.5-year follow-up to determine the incidence of NIDDM. The response rate to the follow-up examination was 77.6%. Subjects who attended the follow-up examination were similar to those who did not attend the follow-up examination in terms of age, sex, and self-

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HOMA, homeostasis model assessment; IR, insulin resistance; WHR, waist-to-hip ratio.

Table 1—*Baseline clinical characteristics of initially nondiabetic subjects by conversion status to NIDDM at follow-up*

	Converters	Nonconverters	*P* value
n	97	1,352	
Age (in years)	47.2 ± 0.76	46.2 ± 0.2	0.003
Impaired glucose tolerance (%)	45.3	11.4	<0.001
BMI (kg/m²)	29.9 ± 0.5	27.9 ± 0.1	0.002
WHR	0.976 ± 0.007	0.968 ± 0.002	0.467
Fasting glucose (mg/dl)	94.8 ± 1.5	85.4 ± 0.3	<0.001
2-h postglucose (mg/dl)	131.7 ± 4.1	103.0 ± 0.8	<0.001
Fasting insulin (μU/ml)*	20.8 (18.0–23.6)	15.3 (14.6–16.1)	<0.001
2-h postinsulin (μU/ml)*	119.0 (100.4–137.5)	92.7 (88.5–96.8)	0.009
Insulin resistance*	4.91 (1.24–5.60)	3.30 (3.12–3.47)	<0.001
β-cell function (%)*	2.1 (1.7–2.5)	3.0 (2.3–4.3)	0.534
Men (%)	43.3	39.9	0.515

The mean ± SE or 95% CI is shown. *Back transformed from log transformation.

reported history of diabetes, myocardial infarction, and smoking. Identical methods were used at both the baseline and the follow-up of the survey.

The HOMA model was developed and validated against hyperinsulinemic-euglycemic clamp (for insulin resistance) and hyperglycemic clamp (for insulin secretion) (10). The formulas are as follows:

$$\text{Insulin resistance (IR)} = \frac{\text{FI} \times \text{G}}{22.5}$$

$$\beta\text{-cell function} = \frac{20 \times \text{FI}}{\text{G} - 3.5}$$

where FI = fasting insulin (μU/ml) and G = fasting glucose (mmol/l).

A total of 22 subjects (1.4%) had fasting glucose levels <3.5 mmol and were excluded from this report (since they had negative calculated β-cell function). Statistical analyses included analyses of variance, χ^2 tests, Spearman correlation coefficients, and multiple logistic regression analyses. The dependent variable in the latter was the development of NIDDM. Fasting insulin, IR (HOMA), and β-cell functions were log transformed to improve skewness and kurtosis. Since fasting insulin and IR were very highly correlated ($r = 0.98$, $P < 0.001$), we did not fit these variables in the same regression model. HOMA β-cell function was also correlated ($P < 0.001$) with both fasting insulin ($r = 0.68$) and HOMA IR ($r = 0.54$), although these correlations were weaker than correlation of HOMA IR with fasting insulin. Since the level of insulin secretion may depend on the level of IR in nondiabetic subjects (13), we fit HOMA β-cell function and IR both separately and simultaneously in the same multiple logistic regression model.

RESULTS — Table 1 shows the clinical and metabolic characteristics of subjects by conversion status. Out of 1,449 subjects, 97 developed diabetes in 3.5 years. Factors associated with conversion status included overall adiposity, higher fasting and 2-h glucose, fasting and 2-h insulin, IR (HOMA), and impaired glucose tolerance. However, age, sex, WHR, and β-cell function (HOMA) were not significantly associated with conversion to NIDDM. Among subjects with impaired glucose tolerance at baseline, 23.4% (44 of 188) developed NIDDM at follow-up compared with 4.4% (53 of 1,261) of subjects with normal glucose tolerance at baseline.

Table 2 shows multiple logistic regression analyses with the development of diabetes as the dependent variable. Three different sets of adjustments were used: model 1: adjusted for age and sex; model 2: adjusted for age, sex, BMI, and WHR; and model 3: adjusted for age, sex, BMI, WHR, and glucose tolerance status. For each set of adjustments, four different regression models were tested (A–D). In models A–C, fasting insulin, insulin resistance, and β-cell function are entered into separate regression models. In model D, both insulin resistance and β-cell function are entered into the same regression model. After adjustment for age and sex, fasting insulin (model A) and insulin resistance (model B) are both highly predictive

Table 2—*Multiple logistic regression analyses of development of type II diabetes in Mexico City applying HOMA model*

Risk factor	Odds ratio	95% CI	Wald χ^2	*P* value
Model 1: adjusted for age and sex				
A) Fasting insulin	3.40	2.54–4.55	21.6	<0.001
B) Insulin resistance	6.16	3.52–6.15	31.5	<0.001
C) β-cell function	0.90	0.84–1.45	0.5	0.478
D) Insulin resistance*	4.89	3.04–7.86	43.0	<0.001
β-cell function†	0.35	0.22–0.56	19.2	<0.001
Model 2: adjusted for age, sex, BMI, and WHR				
A) Fasting insulin	1.78	1.28–2.48	11.9	0.001
B) Insulin resistance	2.04	1.50–2.79	20.4	<0.001
C) β-cell function	0.93	0.69–1.26	0.2	0.658
D) Insulin resistance*	4.45	2.74–7.22	36.6	<0.001
β-cell function†	0.34	0.21–0.55	19.7	<0.001
Model 3: adjusted for age, sex, BMI, WHR, and IGT status				
A) Fasting insulin	1.49	1.04–2.12	4.8	0.028
B) Insulin resistance	1.64	1.17–2.29	8.3	0.004
C) β-cell function	0.99	0.72–1.36	0.0	0.969
D) Insulin resistance*	2.76	1.65–4.61	15.0	<0.001
β-cell function†	0.50	0.30–0.82	7.5	0.006

All risk factors shown in the table are log transformed. *Adjusted also for β-cell function; †adjusted also for insulin resistance. Odds ratio were calculated at the 10th and 90th percentile for risk factors. A) fasting insulin (μU/ml): 10%, 5.0 and 90%, 29.5; B) HOMA IR: 10%, 1.0 and 90%, 6.8; C) HOMA β-cell function: 10%, 82.4 and 90%, 69.

of conversion to diabetes although insulin resistance has a somewhat higher Wald χ^2 than fasting insulin. β-cell function is not a significant predictor of diabetes when entered on its own (model C), but low insulin secretion does significantly predict conversion to diabetes after insulin resistance is also entered into the regression (model D). The predictive power of insulin resistance also increases in model D. This points out the importance of considering both insulin secretion and resistance simultaneously in evaluating risk of NIDDM. After further adjustments for BMI, WHR, and glucose tolerance, these results were very similar.

CONCLUSIONS — We have shown that HOMA IR strongly predicts the development of NIDDM. This association is statistically independent of obesity, body fat distribution, and glucose tolerance status. As is obvious from the high correlation between fasting insulin and the HOMA IR, fasting insulin is also a strong predictor of NIDDM. The HOMA IR measure was, however, a slightly stronger predictor of the NIDDM than was fasting insulin as assessed by the Wald χ^2 test (Table 2).

Decreased β-cell function did not significantly predict the development of NIDDM when used in models that did not include IR or fasting insulin. However, after insulin resistance was included in a multiple logistic regression model, decreased β-cell function became a strong predictor of NIDDM. This suggests that to properly assess β-cell function, the degree of IR needs to be taken into account, i.e., low insulin secretion may be adequate or indeed physiological for an insulin-sensitive patient, but the same level of β-cell function may be inadequate for an insulin-resistant patient.

This report is the first study of predictors of NIDDM in Mexico. Mexicans have an increased prevalence of NIDDM compared with the overall NIDDM population, although their rates are somewhat lower than those of low-income Mexican-Americans in San Antonio, who are also more obese (11). Nondiabetic Mexicans have a degree of hyperinsulinemia comparable to nondiabetic low-income Mexican-Americans in San Antonio (11). The rate of conversion to NIDDM in Mexicans in this middle-aged population is ~2.0% per year. In this population, overall adiposity and impaired glucose tolerance were also risk factors for NIDDM.

This study has several limitations. We were not able to compare HOMA IR to more sophisticated measures of IR such as the hyperinsulinemic-euglycemic clamp or the intravenous glucose tolerance test, nor do we have information on other measures of insulin secretion such as hyperglycemic clamp or the acute insulin response to intravenous glucose. Previous data have suggested that fasting insulin is a good surrogate for insulin resistance (14,15). Since HOMA IR and fasting insulin are extremely highly correlated (r = 0.98), further separate validation of the HOMA IR is probably unnecessary. Several studies have explored correlations of the HOMA IR with hyperinsulinemic-euglycemic clamp (10,15). More important is whether the HOMA β-cell is correlated with impaired insulin secretion. We have recently compared the HOMA β-cell to the ratio of change in insulin to change in glucose over the first 30 min of an oral glucose tolerance test ($\Delta I_{30}/\Delta G_{30}$) (16), which is a direct measure of insulin secretion, since unlike HOMA β-cell function, it incorporates stimulated insulin levels. Also, $\Delta I_{30}/\Delta G_{30}$ recently has been shown to be a good predictor of NIDDM in Mexican-Americans (6) and other populations (8,9). We have recently reported that the HOMA β-cell function is correlated with $\Delta I_{30}/\Delta G_{30}$ in the overall San Antonio Heart Study population (n = 2,735, r = 0.39), as well as in Mexican-Americans (r = 0.41), non-Hispanic whites (r = 0.33), NIDDM subjects (r = 0.40), and nondiabetic subjects (r = 0.34) (all $P < 0.001$). In each of the groups, $\Delta I_{30}/\Delta G_{30}$ was correlated more strongly with HOMA β-cell function than with fasting insulin confirming that HOMA β-cell function 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 (17,18) and perhaps in impaired glucose tolerance as well (17,19). However, the ratio of fasting proinsulin to specific insulin in San Antonio Mexican-Americans with impaired glucose tolerance (17) is only slightly higher than in subjects with normal glucose tolerance (0.09 vs. 0.07, respectively) and still relatively low (17). Proinsulin is thus unlikely to confound our measurement of insulin in nondiabetic subjects.

In conclusion, we have shown using the HOMA assessment that both increased insulin resistance and decreased β-cell function predict the development of NIDDM. The predictive value of decreased β-cell function was greatly strengthened by adjusting for insulin resistance. The HOMA model may provide a useful addition to assessing risk of diabetes in epidemiological studies, but further assessment in other populations is necessary, particularly studies with more sophisticated measures of insulin secretion and resistance.

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