

Oral Disposition Index Predicts the Development of Future Diabetes Above and Beyond Fasting and 2-h Glucose Levels

KRISTINA M. UTZSCHNEIDER, MD^{1,2}
RONALD L. PRIGEON, MD^{3,4}
MIRJAM V. FAULENBACH, MD^{1,2}
JENNY TONG, MD, MPH^{1,2}
DARCY B. CARR, MD, MS⁵

EDWARD J. BOYKO, MD, MPH⁶
DONNA L. LEONETTI, PHD⁷
MARGUERITE J. MCNEELY, MD²
WILFRED Y. FUJIMOTO, MD²
STEVEN E. KAHN, MB, CHB^{1,2}

OBJECTIVE — We sought to determine whether an oral disposition index (DI_O) predicts the development of diabetes over a 10-year period. First, we assessed the validity of the DI_O by demonstrating that a hyperbolic relationship exists between oral indexes of insulin sensitivity and β -cell function.

RESEARCH DESIGN AND METHODS — A total of 613 Japanese-American subjects (322 men and 291 women) underwent a 75-g oral glucose tolerance test (OGTT) at baseline, 5 years, and 10 years. Insulin sensitivity was estimated as $1/\text{fasting insulin}$ or homeostasis model assessment of insulin sensitivity (HOMA-S). Insulin response was estimated as the change in insulin divided by change in glucose from 0 to 30 min ($\Delta I_{0-30}/\Delta G_{0-30}$).

RESULTS — $\Delta I_{0-30}/\Delta G_{0-30}$ demonstrated a curvilinear relationship with $1/\text{fasting insulin}$ and HOMA-S with a left and downward shift as glucose tolerance deteriorated. The confidence limits for the slope of the \log_e -transformed estimates included -1 for $\Delta I_{0-30}/\Delta G_{0-30}$ versus $1/\text{fasting insulin}$ for all glucose tolerance groups, consistent with a hyperbolic relationship. When HOMA-S was used as the insulin sensitivity measure, the confidence limits for the slope included -1 only for subjects with normal glucose tolerance (NGT) or impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) but not diabetes. On the basis of this hyperbolic relationship, the product of $\Delta I_{0-30}/\Delta G_{0-30}$ and $1/\text{fasting insulin}$ was calculated (DI_O) and decreased from NGT to IFG/IGT to diabetes ($P < 0.001$). Among nondiabetic subjects at baseline, baseline DI_O predicted cumulative diabetes at 10 years ($P < 0.001$) independent of age, sex, BMI, family history of diabetes, and baseline fasting and 2-h glucose concentrations.

CONCLUSIONS — The DI_O provides a measure of β -cell function adjusted for insulin sensitivity and is predictive of development of diabetes over 10 years.

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Type 2 diabetes is characterized by both insulin resistance and β -cell dysfunction (1). Abnormalities in β -cell function are present in high-risk individuals long before they develop hy-

perglycemia (1). This recognition has occurred in part because of a better understanding of the ability of the β -cell to regulate its insulin response to stimuli based on differences in insulin sensitivity.

From the ¹Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, Veterans Affairs Puget Sound Health Care System, Seattle, Washington; the ²Department of Medicine, University of Washington, Seattle, Washington; the ³Geriatric Research Education and Clinical Center, Baltimore Veterans Affairs Medical Center, Baltimore, Maryland; the ⁴Division of Gerontology, University of Maryland School of Medicine, Baltimore, Maryland; the ⁵Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Washington, Seattle, Washington; the ⁶Epidemiologic Research and Information Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington; and the ⁷Department of Anthropology, University of Washington, Seattle, Washington.

Corresponding author: Kristina M. Utzschneider, kutzschn@u.washington.edu.

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Using intravenous testing, subjects with normal β -cell function demonstrate a hyperbolic relationship between insulin sensitivity and insulin responses (2,3), consistent with a classic feedback loop. On the basis of this hyperbolic relationship, the product of these two variables, referred to as the disposition index, can be calculated and has highlighted the inability of the β -cell to compensate for insulin resistance in subjects at risk for diabetes (4,5) and with higher fasting glucose levels (6–8). In prospective studies, the disposition index declines well before glucose levels rise into the diabetic range (9). Thus, a low disposition index is an early marker of inadequate β -cell compensation.

This hyperbolic relationship has been demonstrated between measures of insulin sensitivity and response derived from intravenous tests (3) as well as between the early insulin response during an oral glucose tolerance test (OGTT) and insulin sensitivity derived from intravenous testing (10). However, intravenous tests are time-consuming, expensive, and not practical for large studies. The OGTT is less precise (11) but simpler to perform and is often used in large epidemiological or intervention studies. Recently, a nonlinear function describing the relationship between the oral glucose-induced early insulin response and insulin sensitivity has been used to assess β -cell function in both observational (12) and interventional studies (13). Using OGTT measures, Retnakaran et al. (14) were able to show a hyperbolic relationship between insulin sensitivity (Matsuda index) and the incremental area under the curve insulin/glucose ($\text{incAUC}_{\text{ins}/\text{glu}}$) response but not the early insulin response. Sakaue et al. (15) also failed to demonstrate a hyperbolic relationship between OGTT-derived insulin sensitivity and the early insulin response. However, the latter regression analysis failed to account for measurement error in the independent variable, which leads to an underestimation of the slope (16).

We first tested whether the relationship between the early insulin response or the incAUC_{ins/glu} response after oral glucose and surrogate measures of insulin sensitivity were related in a hyperbolic manner using a regression technique that takes measurement error in both variables into account. We then tested whether this relationship exists for different glucose tolerance categories. Finally, as we found the relationship to be hyperbolic, we examined whether a composite measure (oral disposition index) is associated with the development of diabetes.

RESEARCH DESIGN AND METHODS

The Japanese American Community Diabetes Study was conducted in King County, Washington, with baseline testing performed between 1983 and 1988 and follow-up examinations ~5 and 10 years later. The design and methods used in this study have been described previously (17). The study was approved by the local institutional review board, and written informed consent was obtained from each participant.

Baseline oral glucose tolerance testing was performed in 658 subjects; 640 subjects had complete data for insulin and glucose values at basal, 30 min, and 120 min. Ten subjects were excluded because of negative or zero $\Delta I_{0-30}/\Delta G_{0-30}$ ($n = 7$) or incAUC_{ins/glu} responses ($n = 3$). Seventeen subjects were excluded as outliers (see STATISTICAL METHODS). Subjects who did not have diabetes at baseline ($n = 498$) had follow-up examinations and OGTTs at 5 or 6 years (5 year, $n = 448$) and at 10 or 11 years (10 year, $n = 398$).

Study procedures and assays

A standard 75-g OGTT was performed in the morning after a 10-h overnight fast. Samples were drawn just before and at 30, 60, and 120 min after ingestion of glucose. Samples were collected in EDTA, separated, and stored at -20°C before being assayed. Plasma glucose was measured by the glucose oxidase method. Plasma insulin was measured using a modified double-antibody radioimmunoassay as described previously (17). Height, weight, and abdominal circumference (umbilicus) were measured three times at each visit, and the average for each visit was used.

Classification of glucose tolerance

Using the 2003 American Diabetes Association criteria (18), subjects were categorized as having normal glucose tolerance

(NGT) (fasting plasma glucose [FPG] <5.56 mmol/l and 2-h plasma glucose <7.78 mmol/l), impaired glucose metabolism (IGM) (either impaired fasting glucose [IFG]: FPG 5.56–6.99 mmol/l and/or impaired glucose tolerance [IGT]: 2-h plasma glucose 7.78–11.10 mmol/l) or diabetes (FPG ≥ 7.0 mmol/l and/or 2-h plasma glucose ≥ 11.11 mmol/l).

Calculations

Insulin sensitivity was estimated by two methods: 1) 1/fasting insulin or 2) homeostasis model assessment (HOMA) of insulin sensitivity (HOMA-S) using the Web-based HOMA calculator for nonspecific insulin (<http://www.dtu.ox.ac.uk>) (19). The early insulin response was calculated as the ratio of the change in insulin to the change in glucose from 0 to 30 min ($\Delta I_{0-30}/\Delta G_{0-30}$). The incAUC_{ins/glu} response was calculated by the trapezoidal method from 0 to 120 min. The composite measure of β -cell function, which we have termed the oral disposition index (DI_O), was calculated as $\Delta I_{0-30}/\Delta G_{0-30} \times 1/\text{fasting insulin}$.

Statistical analysis

To determine whether the relationships between the dependent ($\Delta I_{0-30}/\Delta G_{0-30}$ or incAUC_{ins/glu}) and independent (1/fasting insulin or HOMA-S) variables were consistent with a rectangular hyperbola ($x \times y = \text{constant}$), we estimated $\ln(\Delta I_{0-30}/\Delta G_{0-30}$ or incAUC_{ins/glu}) as a linear function of $\ln(1/\text{fasting insulin or HOMA-S})$ using regression analysis. If the hyperbolic relationship exists, the slope of the regression line should not be significantly different from -1 . When error is present in both x and y variables, the slope that is determined by ordinary least-squares regression is underestimated because it assumes all error in the y variable. The regression method we used corrects this bias by incorporation of a factor computed as the ratio of the variances of the error in the y to x variables (16). The error estimates for these measurements (57.1% for $\Delta I_{0-30}/\Delta G_{0-30}$, 24.9% for incAUC_{ins/glu}, 16.6% for 1/fasting insulin, and 16.4% for HOMA-S) were based on the day-to-day coefficients of variation in a group of subjects with various glucose tolerance (11). A hyperbolic relationship was presumed if the 95% CI of the slope included -1 . The 95% CI was calculated using the bootstrap method. Subjects were subdivided for analysis by glucose tolerance category. The y intercept of the regression

line of the \ln -transformed variables was calculated, assuming a slope of -1 .

Because outlying values can have marked adverse effects on regression parameters, the data were subjected to a series of tests for influential values, specifically, Cooks distance, DFBETA, DFFIT, COVRatio, and HATvalue using the R statistical procedure “influence measures” (20). Because of the high number of data points, the critical value for each test was set such that the α (type 1 error) was <0.002 . A data point that was identified as an influential point by any of these tests was reviewed graphically, and the subject was eliminated from further analysis.

To exclude the possibility that the regression is artifactual—driven by fasting insulin and glucose appearing in both the insulin sensitivity and $\Delta I_{0-30}/\Delta G_{0-30}$ equations—the same regression procedures were performed on the data except that the 30-min insulin values were shuffled using the Fisher-Yates algorithm to remove any physiological relationship. This shuffle-regression procedure was repeated 100,000 times, and the median and 95% CIs were determined. These simulations showed that only a weak, positive slope resulted with wide confidence limits that did not include -1 [subjects with NGT: $\ln(\text{HOMA-S})$ vs. $\ln(\Delta I_{0-30}/\Delta G_{0-30}) = +0.53$ (0.13–0.94); $\ln(1/\text{fasting insulin})$ vs. $\ln(\Delta I_{0-30}/\Delta G_{0-30}) = +0.46$ (0.11–0.82)].

Statistical analysis was performed using STATA (version 9.0; StataCorp, College Station, TX). Variables that were not normally distributed were \log_e transformed to achieve a normal distribution. ANOVA with a post hoc Scheffe correction was performed to compare variables between different glucose tolerance categories. Multiple logistic regression analysis was performed to determine whether DI_O was independently associated with cumulative diabetes (yes/no) at 10 years. Only subjects without diabetes at baseline were included in this analysis. A diagnosis of diabetes at 5 years was carried forward and included in the cumulative 10-year incidence. The model included $\ln(\text{DI}_O)$, $\ln(\text{age})$, sex, $\ln(\text{BMI})$, $\ln(\text{fasting glucose})$, and $\ln(2\text{-h glucose})$. In addition, subjects without diabetes at baseline were divided into quintiles of baseline DI_O, and the multiple logistic regression analysis was rerun.

To determine whether DI_O was a better predictor of diabetes than 1/fasting insulin or $\Delta I_{0-30}/\Delta G_{0-30}$ alone, nonparametric receiver operating characteristic (ROC) curve

Table 1—Subject characteristics by glucose tolerance category

	NGT	iIFG	iIGT	IFG + IGT	IGM	Diabetes
n	244	60	118	76	254	115
Age (years) (mean ± SD)	48.6 ± 11.9	56.4 ± 10.7	54.0 ± 11.5	59.1 ± 9.5§	56.1 ± 10.9*	61.1 ± 7.4*
Sex (female/male)	120/124	20/40	79/39†	23/53§	122/132	49/66
BMI (kg/m ²)	23.5 ± 0.2	24.7 ± 0.3	23.7 ± 0.3	25.8 ± 0.4§	24.6 ± 0.2*	25.7 ± 0.3*
Abdominal circumference (cm)	84.0 ± 0.51	87.7 ± 0.8	85.5 ± 0.9	90.0 ± 0.9§	87.6 ± 0.5*	91.0 ± 0.8*
FPG (mmol/l)	4.89 (0.58)	5.72 (0.39)	5.06 (0.50)†	5.89 (0.39)§	5.56 (0.72)*	7.56 (3.33)*
2-h plasma glucose (mmol/l)	6.22 (1.44)	6.94 (1.08)	8.69 (1.11)†	9.19 (1.78)‡§	8.47 (1.56)*	15.17 (8.56)*
Fasting insulin (pmol/l)	66 (36)	81 (48)	69 (48)	78 (51)	78 (54)*	102 (96)*
HOMA-S	81.9 (45.2)	63.9 (36.4)	79.2 (50.2)	65.8 (38.8)	70.7 (46.9)*	47.0 (44.7)*
$\Delta I_{0-30}/\Delta G_{0-30}$ (pmol/mmol)	105.7 (102.5)	100.2 (101.9)	81.7 (92.6)	77.9 (65.0)	80.9 (86.5)*	29.9 (41.4)*
incAUC _{ins/glu} (pmol/mmol)	148.6 (138.6)	138.5 (146.5)	104.3 (83.8)†	105.6 (77.8)‡	113.3 (90.8)*	33.8 (49.0)*

Data are reported as mean ± SEM or median (interquartile range) unless otherwise specified. *P < 0.001 NGT versus IGM versus diabetes; †iIFG versus iIGT, ‡iIFG versus IFG + IGT, §iIGT versus IFG + IGT, P < 0.05.

analysis was performed with cumulative diabetes at 10 years (no) as the outcome variable. An optimal cut point for DI_O was obtained using the Youden index (maximum [sensitivity + specificity - 1]). P < 0.05 was considered statistically significant.

RESULTS— The 613 subjects were categorized by glucose tolerance on the basis of their fasting and 2-h plasma glucose measurements (Table 1). Fasting insulin, HOMA-S, and $\Delta I_{0-30}/\Delta G_{0-30}$ did not differ between isolated IFG (iIFG), isolated IGT (iIGT), and IFG + IGT groups. Thus, these groups were combined for analysis into the IGM group. Age, BMI, and abdominal circumference increased progressively with deteriorating glucose metabolism, whereas insulin sensitivity and insulin responses decreased progressively from NGT to IGM to diabetes (Table 1).

Hyperbolic relationship between insulin sensitivity and insulin responses in subjects with NGT

The 95% CI for the regression slopes included -1 for the relationship between ln(1/fasting insulin) and both ln($\Delta I_{0-30}/\Delta G_{0-30}$) (slope -0.87 [95% CI -1.13 to -0.61]) (Fig. 1A) and ln(incAUC_{ins/glu}) (-1.82 [-0.97 to -0.66]). The same analyses were performed substituting HOMA-S for fasting insulin with similar results [ln($\Delta I_{0-30}/\Delta G_{0-30}$) vs. ln(HOMA-S): -0.91 (-1.12 to -0.62)]; ln(incAUC_{ins/glu}) vs. ln(HOMA-S) -2.06 (-3.38 to -0.75)]. For all regressions in subjects with NGT, the slopes included -1 in keeping with a hyperbolic relationship.

Hyperbolic relationship between insulin sensitivity and insulin responses in subjects with IGM and diabetes

In subjects with IGM, the corrected slopes included -1 for both the relationship between ln($\Delta I_{0-30}/\Delta G_{0-30}$) and ln(1/fasting insulin) (-0.84 [95% CI -1.05 to -0.63]) (Fig. 1B) and between ln(incAUC_{ins/glu}) and ln(1/fasting insulin) (-1.27 [-1.68 to -0.86]). Similar results were found when HOMA-S was substituted for 1/fasting insulin (data not shown). When analyzed for each individual IGM group, the relationship between ln($\Delta I_{0-30}/\Delta G_{0-30}$) and ln(1/fasting insulin) was hyperbolic for the iIGT group (-1.15 [-1.43 to -0.87]) and the IFG + IGT group (-0.76 [-1.08 to -0.44]) but not for the iIFG group (-0.47 [-0.89 to -0.06]). Similar results were found when HOMA-S was substituted for 1/fasting insulin (data not shown). The slopes for the relationship with ln(incAUC_{ins/glu}) included -1 for the iIFG and IFG + IGT groups but not for the iIGT group using either 1/fasting insulin or HOMA-S (data not shown).

In those with diabetes, the corrected slopes included -1 for the relationship between ln($\Delta I_{0-30}/\Delta G_{0-30}$) and ln(1/fasting insulin) (-0.76 [-1.16 to -0.35]) (Fig. 1C) and between ln(incAUC_{ins/glu}) and ln(1/fasting insulin) (-2.33 [-3.97 to -0.69]). Use of ln(HOMA-S) in place of ln(1/fasting insulin) resulted in a flatter slope that did not include -1 for ln($\Delta I_{0-30}/\Delta G_{0-30}$) (-0.55 [-0.97 to -0.12]) and a slope that did include -1 but had a very wide CI for ln(incAUC_{ins/glu}) (-2.74 [-5.82 to 0.35]).

The hyperbolic curves demonstrated a shift to the left and downward from NGT to IGM to diabetes ($\Delta I_{0-30}/\Delta G_{0-30}$ versus 1/fasting insulin) (Fig. 1D). Similar shifts were seen when HOMA-S or incAUC_{ins/glu} was used. This decrease in β -cell function is best evaluated by examination of the y intercepts for the ln-ln relationships. These intercepts decreased from NGT (mean ± SD 0.53 ± 0.63) to IGM (0.09 ± 0.61) to diabetes (-1.36 ± 0.99) for ln($\Delta I_{0-30}/\Delta G_{0-30}$) versus ln(1/fasting insulin). Similar decreases were seen for ln($\Delta I_{0-30}/\Delta G_{0-30}$) versus ln(HOMA-S) (NGT 9.12 ± 0.63, IGM 8.66 ± 0.61, and diabetes 7.13 ± 1.04), ln(incAUC_{ins/glu}) versus ln(1/fasting insulin) (NGT 0.82 ± 0.62, IGM 0.39 ± 0.52, and diabetes -1.15 ± 0.98), and ln(incAUC_{ins/glu}) and ln(HOMA-S) (NGT 9.42 ± 0.62, IGM 8.97 ± 0.52, and diabetes 7.34 ± 1.05) (P < 0.005 for all comparisons).

On the basis of the hyperbolic relationship between $\Delta I_{0-30}/\Delta G_{0-30}$ and 1/fasting insulin, the product of these two variables (DI_O) was computed as a composite measure of β -cell function. DI_O decreased progressively from NGT to IGM to diabetes (P < 0.001 for all comparisons) (Fig. 2A). Similar results were obtained when DI_O was calculated using HOMA-S instead of 1/fasting insulin (data not shown). When DI_O was compared among the three IGM groups (iIFG median 1.15 [interquartile range 0.96], iIGT 1.07 [0.82], and IFG + IGT 0.89[0.77] mM⁻¹), DI_O was lower in the IFG + IGT group than in the iIFG group (P = 0.01) or iIGT group (P = 0.051) but did not differ significantly between the iIFG and iIGT groups.

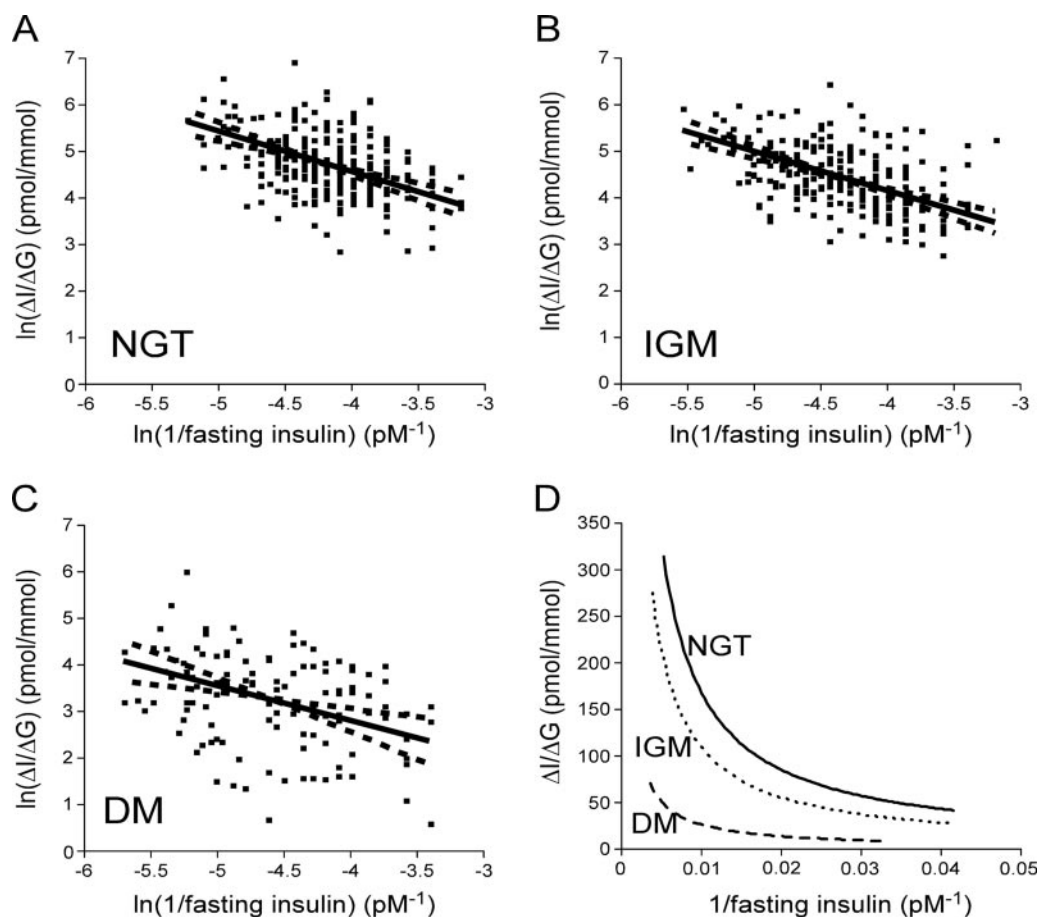


Figure 1—The computed slopes (—) and 95% CIs for the slopes (---) for $\ln(\Delta I_{0-30}/\Delta G_{0-30})$ versus $\ln(1/\text{fasting insulin})$ are plotted for subjects with NGT (slope -0.87 [95% CI -1.13 to -0.61]) (A), IGM (-0.84 [-1.05 to -0.63]) (B), and diabetes (DM) (-0.76 [-1.16 to -0.35]) (C). D: The hyperbolic curves for NGT, IGM, and diabetes, assuming a slope of -1 , are plotted for $\Delta I_{0-30}/\Delta G_{0-30}$ versus $1/\text{fasting insulin}$.

DI_O was associated with the development of diabetes over 10 years

Subjects who progressed to diabetes over the 10-year follow-up period (“progressors”: $n = 9$ with baseline NGT and $n = 84$ with baseline IGM) were compared with those who did not progress (“non-progressor”: $n = 235$ with baseline NGT and $n = 170$ with baseline IGM). Baseline DI_O was significantly lower in the progressors versus the nonprogressors (NGT median 0.90 [interquartile range 0.40] vs. 1.72 [1.42] mM^{-1} , $P < 0.05$; IGM 0.85 [0.57] vs. 1.12 [0.94] mM^{-1} , $P < 0.001$). The relationship between insulin sensitivity and insulin response at baseline was shifted downward and to the left in the progressors compared with the nonprogressors (Fig. 2B).

We examined whether DI_O was an independent predictor of the development of diabetes over time. In subjects who did not have diabetes at baseline, a higher DI_O was associated with a decreased risk of diabetes at 10 years (odds ratio [OR] 0.40

[95% CI 0.25 – 0.66], $P < 0.001$) after adjustment for $\ln(\text{age})$, sex, $\ln(\text{BMI})$, $\ln(\text{fasting glucose})$, and $\ln(2\text{-h glucose})$. Family history added to the model was a weak independent predictor of diabetes (1.79 [1.04 – 3.09], $P = 0.03$) but did not change the significance of DI_O (0.41 [0.25 – 0.68], $P < 0.001$). Similar results were obtained when both family history and $\ln(\text{triglycerides})$ were added to the model. When $\ln(1/\text{fasting insulin})$ and $\ln(\Delta I_{0-30}/\Delta G_{0-30})$ were included in the basic model in place of $\ln(\text{DI}_O)$, both were independent predictors of diabetes at the 10-year follow-up: $\ln(1/\text{fasting insulin})$ 0.32 [0.14 – 0.73] and $\ln(\Delta I_{0-30}/\Delta G_{0-30})$ 0.41 [0.25 – 0.68]. Similar results were obtained when HOMA-S was used to compute DI_O (data not shown). When the analysis was restricted to subjects with NGT at baseline, DI_O was still an independent predictor of diabetes (0.24 [0.06 – 0.88], $P = 0.03$).

When the multiple logistic regression analysis was rerun using quintiles of DI_O (categorical variables coded as dummy

variables), the risk for diabetes decreased as DI_O increased (versus quintile 1 [lowest DI_O]: quintile 2 OR 0.63 [95% CI 0.32 – 1.25], $P = 0.19$; quintile 3 0.40 [0.18 – 0.90], $P = 0.03$; quintile 4 0.39 [0.17 – 0.94], $P = 0.04$; and quintile 5 [highest DI_O] 0.14 [0.05 – 0.45], $P = 0.001$). The number of subjects who developed diabetes over the 10 years decreased as the DI_O quintile increased (Fig. 2C).

ROC curve analysis was performed to determine whether the composite measure DI_O was better at predicting protection from diabetes compared with $\Delta I_{0-30}/\Delta G_{0-30}$ or $1/\text{fasting insulin}$ alone. The area under the ROC curve was highest using DI_O (0.86 [95% CI 0.82 – 0.89]), intermediate for $\Delta I_{0-30}/\Delta G_{0-30}$ (0.78 [0.74 – 0.82]), and lowest for $1/\text{fasting insulin}$ (0.65 [0.60 – 0.70]). The area under the ROC curve for DI_O was significantly higher than that for the other two variables ($P < 0.001$ for each) (Fig. 2D). The best predictor for remaining without dia-

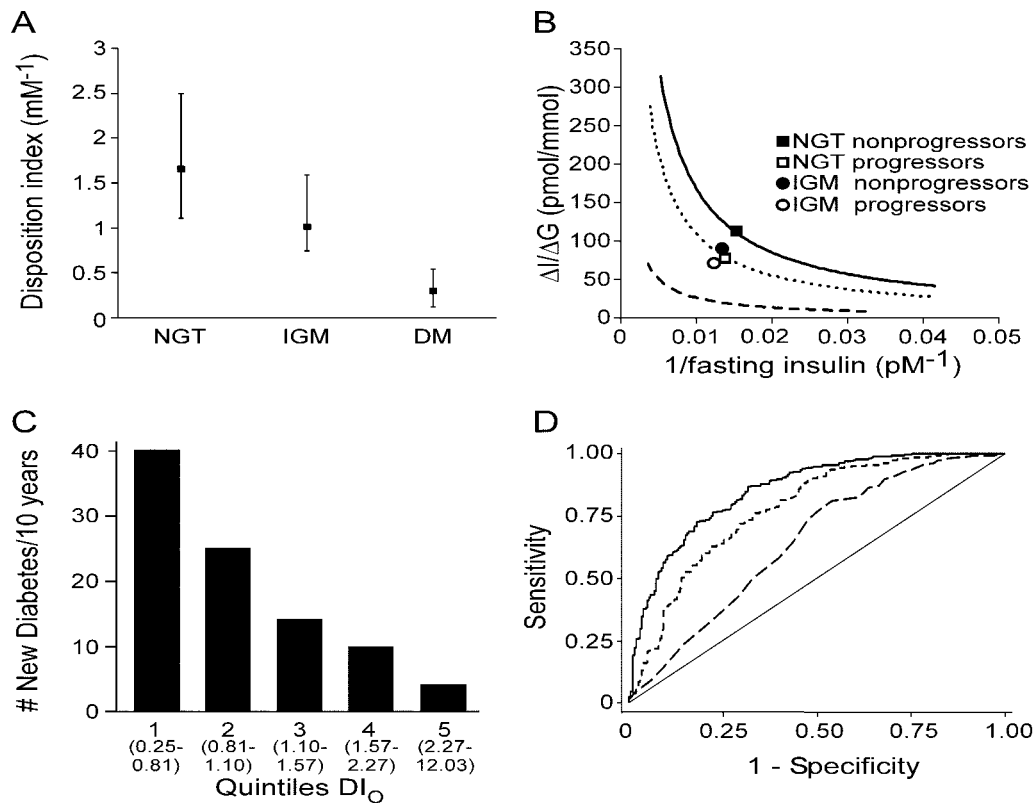


Figure 2—A: The DI_0 ($\Delta I_{0-30}/\Delta G_{0-30} \times 1/\text{fasting insulin}$) decreases from NGT to IGM to diabetes (DM) (median [interquartile range]). B: The logarithmic means for baseline $\Delta I_{0-30}/\Delta G_{0-30}$ and $1/\text{fasting insulin}$ values are plotted for subjects with NGT (■ and □) and IGM (● and ○) as nonprogressors (■ and ●) and progressors (□ and ○) relative to the hyperbolic curves. Progressors had lower β -cell function at baseline. C: The number of subjects who developed diabetes over the 10-year follow-up period by quintiles of baseline DI_0 . D: ROC curves comparing ability of baseline $\Delta I_{0-30}/\Delta G_{0-30}$ (dotted line), $1/\text{fasting insulin}$ (dashed line), and DI_0 (solid line) to predict cumulative diabetes at 10 years.

betes was $DI_0 \geq 1.24$ (sensitivity of 59.3% and specificity of 79.6%).

CONCLUSIONS— A hyperbolic relationship between insulin sensitivity and responses using intravenous measures (3) has been widely accepted. This study demonstrates that measures of insulin sensitivity and response derived from an OGTT are also compatible with a hyperbolic association and that this relationship is present not only in subjects with NGT but also in subjects with IGM and diabetes. Importantly, the existence of this relationship allows calculation of a DI_0 , which was predictive of future development of diabetes above and beyond traditional risk factors, such as family history and fasting and 2-h glucose levels. The DI_0 as a composite measure was a better predictor for diabetes than either $\Delta I_{0-30}/\Delta G_{0-30}$ or $1/\text{fasting insulin}$ alone. Our finding that the relationship between insulin sensitivity and insulin response based on OGTT measures is shifted downward and to the left as glucose tolerance deteriorates is consistent with previous work using intravenous

tests (6,21). With the use of intravenous measures, the disposition index was lower at baseline and declined further in those whose glucose metabolism deteriorated over time (9,21,22). Our current findings extend use of this approach to measure β -cell function using OGTT-derived measures. Importantly, we have shown that the DI_0 was inversely correlated with the risk of future diabetes. Thus, the DI_0 may be useful to help identify subjects in large epidemiological studies who have an increased risk of developing diabetes. The statistical methodology for assessment of this hyperbolic relationship is critical when both the x and y variables are measured with error, as the slope will be underestimated if measurement error in the independent variable is not accounted for (23). The absence of a hyperbolic relationship between these same OGTT measures in a previously published study (15) may have been due to this issue. Although Retnakaran et al. (14) did account for error estimates in both variables, the slopes for the relationships between $\Delta I_{0-30}/\Delta G_{0-30}$ and measures of

insulin sensitivity ($1/\text{HOMA}$ for insulin resistance and the Matsuda index) were < -1 (-1.61 and -1.60 , respectively) and because of the wide CIs that included 0 were not considered to be hyperbolic. In contrast, we found that the slopes for subjects with NGT for the log-relationships between $\Delta I_{0-30}/\Delta G_{0-30}$ and $1/\text{fasting insulin}$ (slope = -0.87) or HOMA-S (slope = -0.91) were slightly > -1 , but the CI still included -1 , consistent with a hyperbolic relationship. Differences in results between our study and that by Retnakaran et al. could be due to differences in error estimates, as the slopes are quite sensitive to changes in error estimates. Of note, our results are consistent with the slope estimates for the log-relationship between the acute insulin response to glucose and the insulin sensitivity index (S_1) derived from a frequently sampled intravenous glucose tolerance test (slope = -0.97) (3) or between $\Delta I_{0-30}/\Delta G_{0-30}$ and S_1 (slope = -0.86) (10). The strengths of this study include the large number of subjects and the longitudinal study design. However, we failed to show a hyperbolic relationship

for some regressions when the iIFG and iIGT groups were examined separately. It is possible that glucose tolerance in these subpopulations fails to follow a hyperbolic relationship, although it seems unlikely because when they are combined the hyperbolic relationship is present. In the group with diabetes, the log-relationships between $\Delta I_{0-30}/\Delta G_{0-30}$ and insulin sensitivity measures were flatter and did not include -1 when HOMA-S was used. This may reflect the much broader range of glucose tolerance (and fasting glucose levels) in this group. Finally, the CIs for the slopes using the $\text{incAUC}_{\text{ins/ glu}}$ ratio, although including -1 , were much wider and thus less reliable. Other limitations include the fact that we excluded 17 subjects (2.7%) with outlier data from this analysis, as outliers can have a disproportionate effect on regression analysis. Finally, this study was performed in Japanese Americans, and, thus, we cannot generalize the conclusions to other ethnic populations, although it is likely that the same physiological feedback processes would occur in other ethnic groups.

There are limitations to application of the DI_O that need to be kept in mind. In particular, because of the increased variability of OGTT measures compared with intravenous testing, the DI_O will be more variable and, hence, appropriately large sample sizes will be needed. Second, it cannot be assumed that all measures of insulin sensitivity or response will follow a hyperbolic pattern and thus simply multiplying any two measures together without first demonstrating a hyperbolic function is not appropriate. Also, it should be kept in mind that the compensatory insulin response includes both changes in insulin secretion as well as adaptations in hepatic insulin extraction (24) and changes in incretin hormone responses that may modulate both insulin secretion and hepatic insulin extraction (25).

In summary, we have demonstrated that use of OGTT-derived measures of insulin response and insulin sensitivity can delineate differences in β -cell function between glucose tolerance categories. Furthermore, the composite measure DI_O can be used to assess β -cell function and was independently associated with future diabetes risk. Thus, the disposition index approach using these specific measures offers a way to assess β -cell function using an OGTT and could be used to identify subjects with poor

β -cell function for intervention trials and to assess the impact of interventions in large clinical studies.

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