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Insulin secretion based on the late oral glucose tolerance test period and incident diabetes: the San Antonio Heart Study

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Abstract

Aims—The Insulinogenic Index from 0 to 30 min ($\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$), a measure of insulin secretion derived from the early period of the oral glucose tolerance test, predicts future diabetes. However, there are few data on secretory measures from the late oral glucose tolerance test period. We therefore investigated the association of the ratio of the area under the insulin curve to the area under the glucose curve from 60 to 120 min ($I/G_{AUC\ 60\text{-}120}$) with incident diabetes.

Methods—Participants were 1540 Mexican Americans and non-Hispanic whites in the San Antonio Heart Study who were free of diabetes at baseline. We analysed indices of sensitivity (Matsuda index) and secretion from the early ($\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$) and late oral glucose tolerance test periods ($I/G_{AUC\ 60\text{-}120}$).

Results—A total of 179 participants developed diabetes after 7.5 years. $I/G_{AUC60\text{-}120}$ was an independent predictor of diabetes [odds ratio × 1 SD unit increase, 0.37 (0.26–0.54)] in a model that also included age, sex, ethnicity, body mass index, family history of diabetes, Matsuda index and ($\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$) as covariates. $I/G_{AUC\ 60–120}$ increased the C statistic (a test of discrimination) of the model (0.882 *vs.* 0.875, $P = 0.044$). $I/G_{AUC\ 60–120}$ correctly reclassified one-fifth of individuals with moderate and strong risks of future diabetes. The net reclassification improvement was 0.13 ($P < 0.001$) and the integrated discrimination improvement was 0.033 ($P < 0.001$).

Conclusions—An insulin secretory measure derived from the late oral glucose tolerance test period is useful for classifying individuals at risk of future diabetes independently of other risk factors, including insulin sensitivity and a secretory measure from the early oral glucose tolerance test period.

Keywords

epidemiology; insulin resistance; insulin secretion; oral glucose tolerance test; prediction of Type 2 diabetes mellitus

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Competing interests
Nothing to declare.

Supporting Information
Additional Supporting Information may be found in the online version of this article.

Introduction

First-phase insulin secretion (acute insulin response) derived from the frequently sampled intravenous glucose tolerance test predict conversion to Type 2 diabetes [1,2]. This test is invasive and costly; therefore, simple surrogate indices of insulin secretion have been developed using insulin and glucose concentrations from the fasting state or the early period of the oral glucose tolerance test (OGTT) (e.g. insulinogenic index from 0 to 30 min ($\Delta I_{0–30}/\Delta G_{0–30}$)]. These surrogate indices are also predictors of future diabetes [3–9]. Another early insulin secretory defect reported in individuals with normal glucose tolerance and a first-degree relative with Type 2 diabetes is reduced second-phase insulin release measured by a clamp technique [10]. Stumvoll *et al.* [11] described insulin secretory indices derived from the OGTT ($S1Ph_{OGTT}$ and $S2Ph_{OGTT}$) that have strong correlations with first- and second-phase insulin release measured by the hyperglycaemic clamp. However, the ability of these indices to detect individuals at risk of future diabetes has not been explored.

β-Cell dysfunction needs to be interpreted in the context of concomitant insulin resistance [12–14]. We hypothesized that indices of insulin secretion originated from the late OGTT period could add predictive information to $\Delta I_{0–30}/\Delta G_{0–30}$. We used simple strategies, such as the change in insulin concentration relative to the change in glucose concentration [15] and the insulin area under the curve (AUC) relative to the glucose AUC [16], to generate indices of secretion from the late OGTT period: (1) the ratio of relative change in insulin concentration to relative change in glucose concentration from 60 min to 120 min ($\Delta I_{60–120}/\Delta G_{60–120}$]; and (2) the ratio of the insulin to glucose concentration areas from 60 to 120 min ($I/G_{AUC\ 60–120}$]. The aim of the present study, therefore, was to analyse the association of insulin secretory indices from the early and late OGTT periods with incident Type 2 diabetes.

Patients and methods

Study population

The San Antonio Heart Study is a longitudinal, epidemiological study designed to study Type 2 diabetes and cardiovascular disease among Mexican Americans and non-Hispanic whites living in San Antonio, Texas, USA. Protocols were approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. Details of the study design have been previously published [17]. Briefly, all Mexican Americans and non-Hispanic whites (men and non-pregnant women) aged 25–64 years that resided in randomly selected households from low-, middle- and high-income census tracts were invited to participate. All subjects gave written informed consent.

We analysed data from cohort 2 participants, because OGTT sampling times at 30 min and 60 min were not available in cohort 1 participants. Baseline data were collected from January 1984 to December 1988 and follow-up data between October 1991 and October 1996 (mean follow-up of 7.5 years; range 6.3–10.3 years). Incident diabetes was ascertained in 1734 of 2459 [70.5%) participants. Relevant information was missing in 194 participants; therefore, this study presents information on 1540 individuals.

Anthropometric measurements were obtained by trained personnel. Blood specimens were collected before (0 min) and 30, 60 and 120 min after a 75 g oral glucose load (Orangedex; Custom Laboratories, Baltimore, MD, USA) to determine glucose and insulin levels. Serum insulin was measured by a radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA) that had a high degree of cross-reactivity with proinsulin (70–100%).

We applied the 2003 American Diabetes Association criteria to define diabetes (fasting glucose ≥ 7.0 mmol/l and/or 2-h glucose ≥ 11.1 mmol/l), impaired glucose tolerance (2-h glucose ≥ 7.8 mmol/l and < 11.1 mmol/l), and normal glucose tolerance (2-h glucose < 7.8 mmol/l). Subjects who reported current treatment with glucose-lowering medications were considered to have diabetes.

We used published formulae to calculate homeostasis model assessment of insulin resistance (HOMA IR; basal insulin × basal glucose/22.5) [18] and Matsuda index [10^4/(basal glucose × basal insulin × mean glucose × mean insulin]$^{0.5}$) [19]. In this last formula, mean glucose and mean insulin concentrations indicate average glucose (mg/dl) and insulin concentrations (mU/l) based on sampling times at 0, 30, 60 and 120 min. Glucose values at 90 min were not available in the San Antonio Heart Study; however, the Matsuda index based on 0, 30 and 120 min sampling times and the original Matsuda index had similar relationship with clamp-derived insulin sensitivity [20].

We also used published formulas for $\Delta I_{0–30}/\Delta G_{0–30}$ (insulin at 30 min − basal insulin/glucose at 30 min − basal glucose) [15], $S1PH_{OGTT}$ [1283 + 1.829 × insulin at 30 min − 138.7 × glucose at 30 min + 3.772 × basal insulin) [11] and $S2PH_{OGTT}$ [287 + 0.4164 × insulin at 30 min − 26.07 × glucose at 30 min + 0.9226 × basal insulin) [11]. The parameter $I/G_{AUC\ 60–120}$ was computed as insulin AUC to glucose AUC from 60 to 120 min. The AUCs were calculated by the trapezoidal method. The parameter $\Delta I_{60–120}/\Delta G_{60–120}$ was computed as 1 − [(insulin at 60 min − insulin at 120 min/insulin at 60 min)/1 − (glucose at 60 min − glucose at 120 min)/glucose at 60 min]. This formula took into account the negative values resulting from calculating insulin and glucose changes (negative values in 40.3% of the estimates). More importantly, the fit of models with $I/G_{AUC\ 60–120}$ (C statistic of a model with the Matsuda index as a covariate, 0.833) was better than that of models with $\Delta I_{60–120}/\Delta G_{60–120}$ (C statistic of a model with Matsuda index as a covariate, 0.785, $P < 0.001$). Thus, $I/G_{AUC\ 60–120}$ was used as the index of insulin secretion during the late OGTT period.

Statistical analyses

Statistical analyses were performed with the SAS statistical software (version 9.2; SAS Institute Inc. Cary, NC, USA). Differences in baseline variables by sex and ethnicity were investigated by two-way analysis of covariance for continuous variables or logistic regression for dichotomous variables. Pearson's partial correlation coefficients were used to analyse the strength of the relationship between variables. Correlation coefficients were compared by the T2 method [21]. The relation of Matsuda index to measures of insulin secretion was also assessed by ordinary least-squares regression as follows: log(secretion measure) = constant + β × log(Matsuda index). We were unable to use a method that accounted for the variability in the measurement of both the dependent and independent variables as previously done for the derivation of both the disposition index (insulin sensitivity index × acute insulin response) on the frequently sampled intravenous glucose tolerance test [13] and insulin secretion-sensitivity index-2 (Matsuda index × insulin AUC to glucose AUC from 0 to 120 min) on OGTT [16]. The risk of future diabetes associated with indices of insulin sensitivity and insulin secretion was determined by logistic regression analysis.

The predictive discrimination was assessed by the C statistic [22]. The C statistic results for different models were compared by bootstrap sampling. We used the Hosmer–Lemeshow goodness-of-fit test, a measure of deviation between observed and expected event rates in deciles of fitted risk values, to assess calibration of a logistic regression model that included age, sex, ethnicity, BMI, family history of diabetes, Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$ before and after the addition of other indices of secretion. Using these two logistic

regression models, we examined measures of reclassification, the net reclassification improvement and the integrated discrimination improvement, to analyse the discriminative value of $I/G_{AUC\ 60\text{-}120}$. The net reclassification improvement takes into account changes in estimated prediction probabilities that involve a change from one category to another [23]. We used clinically relevant a priori categories (< 1%, 1–5.9%, and ≥ 6% yearly risk of diabetes) based on the yearly risk of developing diabetes among San Antonio Heart Study participants who had normal fasting and 2-h glucose concentrations (0.7% per year) or impaired glucose tolerance (6.1% per year). The integrated discrimination improvement evaluates the change in the estimated prediction probabilities for all possible cut-offs [23]. Log-transformed values of insulin levels and indices of insulin resistance/sensitivity and insulin secretion were used to improve discrimination and calibration of the models and to minimize the influence of extreme observations. We considered a P value < 0.050 significant.

Results

Mexican Americans had higher insulin and glucose levels and more adiposity and family history of diabetes than non-Hispanic whites (Table 1). Indices of insulin resistance and secretion were also higher in Mexican Americans. Men had more insulin resistance and central adiposity and higher fasting and 1-h insulin and glucose concentrations than women. Women had more family history of diabetes and higher 2-h insulin and glucose concentrations. Women also had higher insulin secretion, as measured by $\Delta I_{0–30}/\Delta G_{0–30}$, and similar secretion, as measured by the other secretory indices. Ethnicity had an interaction effect on the relation of sex to HOMA IR, Matsuda index, $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$.

Correlations between indices of secretion and with other metabolic variables

We found that $\Delta I_{0–30}/\Delta G_{0–30}$ had a moderate relationship with $I/G_{AUC\ 60–120}$. These two indices had strong correlations with $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$ (Table 2). In addition, $S1Ph_{OGTT}$ was very highly correlated with $S2Ph_{OGTT}$ ($r = 0.99$) and both had similar relationships with all metabolic variables. We found that $\Delta I_{0–30}/\Delta G_{0–30}$ was less strongly related to indices of insulin resistance and measures of adiposity than any of the other secretory indices. All secretory indices had direct correlations with insulin levels (moderate for $\Delta I_{0–30}/\Delta G_{0–30}$, moderately strong for $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$, and strong for $I/G_{AUC\ 60–120}$). Secretory indices differed in their relationships with plasma glucose levels (weakly negative for $\Delta I_{0–30}/\Delta G_{0–30}$ and weakly positive for $I/G_{AUC\ 60–120}$).

Although curvilinear, the relation of the Matsuda index to $\Delta I_{0–30}/\Delta G_{0–30}$ and $I/G_{AUC\ 60–120}$ was not rectangular hyperbolic (exponent parameters differed significantly from −1) using an ordinary least-squares regression (see the Supporting Information, Table S1).

Predictive discrimination of measures of secretion

During a 7.5-year follow-up, 179 of the 1540 (11.6%) participants developed diabetes. The predictive discrimination of the Matsuda index (C statistic = 0.766) was increased by adding to the model any of the indices of insulin secretion: $\Delta I_{0–30}/\Delta G_{0–30}$ (0.851, $P < 0.001$), $I/G_{AUC\ 60–120}$ (0.832, $P < 0.001$), $S1Ph_{OGTT}$ (0.850, $P < 0.001$) or $S2Ph_{OGTT}$ (0.851, $P < 0.001$). The predictive discrimination of a model with the Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$ (C statistic = 0.851) was increased by $I/G_{AUC\ 60–120}$ (0.860, $P = 0.016$), but not by $S1Ph_{OGTT}$ (0.853, $P = 0.368$) or $S2Ph_{OGTT}$ (0.854, $P = 0.250$).

The $I/G_{AUC\ 60–120}$ value increased the C statistic of a model that had the Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$ as independent variables (0.875 *vs.* 0.882, $P = 0.044$) (Table 3). Matsuda

index, $\Delta I_{0–30}/\Delta G_{0–30}$, and $I/G_{AUC\ 60–120}$ were independent predictors even after entering IGT into the model. In contrast, the C statistic was not significantly changed by either $S1Ph_{OGTT}$ (0.877, $P = 0.828$) or $S2Ph_{OGTT}$ (0.877, $P = 0.610$).

Models predicting incident diabetes that contained the product, Matsuda index × $I/G_{AUC\ 60–120}$ or Matsuda index × $\Delta I_{0–30}/\Delta G_{0–30}$, had similar predictive discrimination to those that contained the individual components (see the Supporting Information, Table S2).

Heterogeneity analyses

In a model with the Matsuda index, $\Delta I_{0–30}/\Delta G_{0–30}$ and $I/G_{AUC\ 60–120}$ as independent variables, we examined effect modification by testing the statistical significance of the interaction of sex, ethnicity, family history of diabetes and glucose tolerance status on the relation of Matsuda index, $\Delta I_{0–30}/\Delta G_{0–30}$ or $I/G_{AUC\ 60–120}$ to incident diabetes. All these potential interaction effects had a *P*-value ≥ 0.16, except for interaction terms ethnicity × $\Delta I_{0–30}/\Delta G_{0–30}$ ($P = 0.041$) and ethnicity × $I/G_{AUC\ 60–120}$ ($P = 0.086$). Interaction terms Matsuda index × $\Delta I_{0–30}/\Delta G_{0–30}$, Matsuda index × $I/G_{AUC\ 60–120}$, and $\Delta I_{0–30}/\Delta G_{0–30}$ × $I/G_{AUC\ 60–120}$ were not significant either ($P \geq 0.35$). Matsuda index, $\Delta I_{0–30}/\Delta G_{0–30}$, and $I/G_{AUC\ 60–120}$ were independent predictors of future diabetes in varying categories of age, sex, ethnicity, family history of diabetes, BMI and glucose tolerance (Fig. 1). There were, however, two exceptions: confidence intervals crossed 1.0 with $I/G_{AUC\ 60–120}$ in individuals aged 25–44 years [odds ratio (OR) 0.70 (0.36–1.35)] and with $\Delta I_{0–30}/\Delta G_{0–30}$ in those with IGT [OR 0.59 (0.34–1.01)].

Discrimination

The Hosmer–Lemeshow test yielded a chi-square of 16.1 ($P = 0.041$) for the model without $I/G_{AUC\ 60–120}$ and 9.1 ($P = 0.332$) for the model with $I/G_{AUC\ 60–120}$. This indicates that the model with $I/G_{AUC\ 60–120}$ was better calibrated (higher agreement between observed incidence of diabetes and predictions). Almost one-fifth of individuals with moderate and strong risk of future diabetes were reclassified by the addition of $I/G_{AUC\ 60–120}$ (66 and 98 individuals were properly reclassified to a higher and lower risk category, respectively) (Table 4a). The net reclassification improvement was 0.13 ($P < 0.001$) after the addition of $I/G_{AUC\ 60–120}$ and the integrated discrimination improvement was 0.033 ($P < 0.001$). A statistically significant integrated discrimination improvement indicates that the addition of $I/G_{AUC\ 60–120}$ improved the discriminatory property of the model with age, sex, ethnicity, BMI, family history of diabetes, Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$.

The addition of $I/G_{AUC\ 60–120}$ also had additional value to a different model that included all the independent variables of the previous model plus impaired glucose tolerance (Table 4b). A total of 66 and 69 individuals were correctly reclassified to a higher and lower risk category, respectively. The net reclassification improvement was 0.05 ($P = 0.043$) and the integrated discrimination improvement was 0.018 ($P < 0.001$).

Discussion

The Insulinogenic Index, $I/G_{AUC\ 60–120}$, predicts incident diabetes independently of $\Delta I_{0–30}/\Delta G_{0–30}$. The fit of models is excellent across varying categories of age, sex, family history of diabetes and BMI. Equally good fit is demonstrated in both high-risk Mexican Americans and low-risk non-Hispanic whites as well as in individuals with normal glucose tolerance and in those with impaired glucose tolerance. The index $I/G_{AUC\ 60–120}$ has additional value for predicting incident diabetes beyond the predictive discrimination of Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$.

Most subjects with hyperglycaemia have impaired β-cell function [24]. $\Delta I_{0–30}/\Delta G_{0–30}$, the capacity for insulin response during the early OGTT period, has shown to correlate weakly with first- and second-phase insulin secretion ($r = 0.25$ and $r = 0.22$, respectively) as measured by hyperglycaemic clamp studies [11] and more strongly with first-and second-phase insulin secretion by intravenous glucose tolerance test ($r = 0.58$ and $r = 0.47$, respectively) [20]. $\Delta I_{0–30}/\Delta G_{0–30}$ has been described as a predictor of diabetes in multiple studies [6–8]. The current results indicate that $\Delta I_{0–30}/\Delta G_{0–30}$ is a strong predictor of incident diabetes independently of a measure of insulin secretion derived from the late OGTT period.

Stumvoll *et al.* [11] stated that $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$ had more robust correlations with first- and second-phase insulin release by the hyperglycaemic clamp technique than did $\Delta I_{0–30}/\Delta G_{0–30}$ and homeostasis model assessment of β-cell function. In this study, however, both $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$ had identical relationships with clamp-derived first phase ($r = 0.78$) and second phase ($r = 0.79$) insulin release [11]. This suggests that $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$ are highly correlated, as do our results ($r = 0.99$ for the relationship between $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$). Both indices increase the predictive discrimination of the Matsuda index, but neither of them increases the predictive discrimination of models with $\Delta I_{0–30}/\Delta G_{0–30}$.

Measured by C statistic [25,26], $I/G_{AUC\ 60–120}$ increases the predictive discrimination of the Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$. Measures of calibration and reclassification [27,28], which are more sensitive tests of improvement in model discrimination, also indicate that $I/G_{AUC\ 60–120}$ adds discriminatory value to the Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$. This may be relevant for predicting a future outcome in individuals with a moderate or significant risk. For example, the yearly risk of future diabetes is 1.0% in a hypothetical 50-year-old non-Hispanic white woman who has no family history of diabetes, BMI of 25 kg/m^2, no impaired glucose tolerance, a Matsuda index of 2 and $\Delta I_{0–30}/\Delta G_{0–30}$ of 1.5. The addition of $I/G_{AUC\ 60–120}$ to the prediction model changes the estimated yearly risk of future diabetes to 0.6% if $I/G_{AUC\ 60–120}$ is 1.5 and to 2.5% if $I/G_{AUC\ 60–120}$ is 0.5. A much more relevant change occurs in a 50-year-old non-Hispanic white woman who has no family history of diabetes, BMI of 30 kg/m^2, impaired glucose tolerance, a Matsuda index of 2 and $\Delta I_{0–30}/\Delta G_{0–30}$ of 1.5. The estimated yearly risk is 4.7% according to the model without $I/G_{AUC\ 60–120}$. The addition of this variable changes the yearly risk to 2.3% if $I/G_{AUC\ 60–120}$ is 1.5 and to 9.9% if $I/G_{AUC\ 60–120}$ is 0.5. Consequently, $I/G_{AUC\ 60–120}$ may be useful for the classification of individuals in clinical studies.

The risk estimate that uses $I/G_{AUC\ 60–120}$ is a more accurate image of actual risk for all 164 reclassified participants. The proportion of reclassified individuals at low risk (< 1% per year) is relatively small, but a more significant proportion occurs in those at moderate (1–6% per year) and high risks (≥ 6% per year). Thus, $I/G_{AUC\ 60–120}$ would have a significant effect in the stratification of individuals in a hypothetical population. For example, if the prediction model with age, sex, ethnicity, BMI, family history of diabetes, Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$ is applied to a cohort of 100 000 individuals without diabetes from San Antonio, 59 600 of them will be considered at low risk (< 1% yearly risk), 34 200 at moderate risk (1–5.9% yearly risk) and 6200 at high risk (≥ 6% yearly risk) for developing diabetes. The addition of $I/G_{AUC\ 60–120}$ will reclassify 10 951 individuals: from the low-risk category, 2861 will now be considered at moderate risk; from the moderate-risk category, 5404 will now be at low risk and 1539 at high risk; and from the high-risk category, 1147 will be at moderate risk. Thus, $I/G_{AUC\ 60–120}$ may have discriminatory value in epidemiological studies.

The relationship between acute insulin response and insulin sensitivity index, two measures derived from the frequently sampled intravenous glucose tolerance test, is hyperbolic [13,16]. A similar relationship has been described between two indices derived from the OGTT, insulin AUC to glucose AUC from 0 to 120 min and Matsuda index [16,29]. The product of these two indices, insulin secretion-sensitivity index-2, has a stronger association with the disposition index than products involving $\Delta I_{0–30}/\Delta G_{0–30}$ [29]. Unable to take into account the variability in the measurement of Matsuda index and $I/G_{AUC\ 60–120}$ [13,16], our study cannot determine whether the relationship between these two indices is rectangular hyperbolic. However, our results indicate that the product, Matsuda index × $I/G_{AUC\ 60–120}$ or Matsuda index × $\Delta I_{0–30}/\Delta G_{0–30}$, does not improve the ability to predict future diabetes of the individual components, as previously reported using direct measures [30].

In summary, measures of insulin secretion derived from the early and late OGTT periods are independent predictors of Type 2 diabetes. This holds in different subgroups including ethnic and glucose tolerance categories. As the OGTT is relatively easy to perform, insulin secretory indices from the early and late OGTT periods may be useful for understanding the natural history of diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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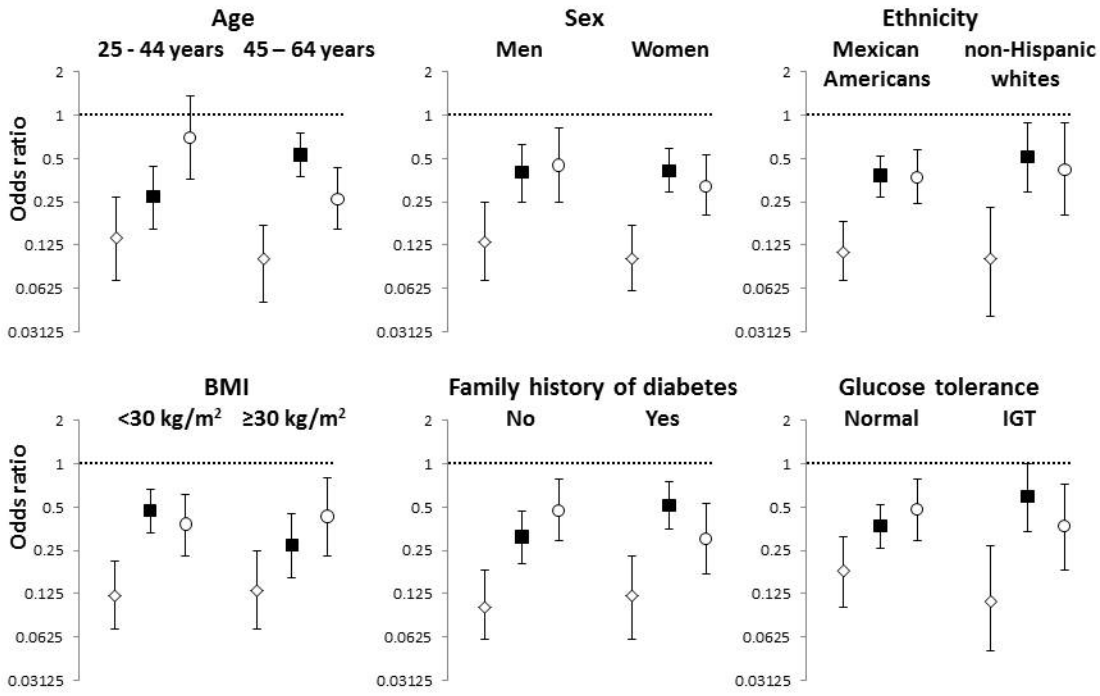

FIGURE 1.

Diabetes risk associated with Matsuda index, $\Delta I_{0–30}/\Delta G_{0–30}$ (insulinogenic index from 0 to 30 min) and $I/G_{AUC\ 60–120}$ (ratio of area under the insulin curve to area under the glucose curve from 60 to 120 min) stratified by age, sex, ethnicity, BMI, family history of diabetes and glucose tolerance status. Open diamonds, Matsuda index; closed square, $\Delta I_{0–30}/\Delta G_{0–30}$; open circle, $I/G_{AUC\ 60–120}$. Age, sex, ethnicity, BMI, family history of diabetes, Matsuda index, $\Delta I_{0–30}/\Delta G_{0–30}$ and $I/G_{AUC\ 60–120}$ were included in all models. The panels present the odds ratio reflecting the change in risk of future diabetes for one standard deviation unit increase. IGT, impaired glucose tolerance.

Table 1

Age-adjusted baseline characteristics by sex and ethnic origin

	Non-Hispanic whites		Mexican Americans		Ethnicity (*P*)	Sex (*P*)	Ethnicity × sex interaction (*P*)
	Men	**Women**	**Men**	**Women**			
n	242	268	425	605			
Age [*]	44.1 ± 0.7	43.5 ± 0.7	42.6 ± 0.5	43.7 ± 0.4	0.367	0.360	0.145
BMI (kg/m^2)	26.9 ± 0.3	25.5 ± 0.3	28.2 ± 0.2	28.7 ± 0.2	< 0.001	0.637	< 0.001
Waist circumference (cm)	96.0 ± 0.8	81.5 ± 0.8	94.9 ± 0.6	87.2 ± 0.5	< 0.001	< 0.001	< 0.001
Family history of diabetes (%)	14.4 (10.5–19.5)	20.1 (15.7–25.3)	35.1 (30.7–39.7)	42.2 (38.3–46.9)	< 0.001	0.005	0.724
Fasting glucose (mmol/l)	4.82 ± 0.04	4.63 ± 0.03	4.87 ± 0.03	4.72 ± 0.02	0.024	< 0.001	0.516
1-h glucose (mmol/l)	7.55 ± 0.14	6.72 ± 0.13	7.90 ± 0.10	7.23 ± 0.09	< 0.001	< 0.001	0.501
2-h glucose (mmol/l)	5.21 ± 0.11	5.59 ± 0.10	5.69 ± 0.08	6.25 ± 0.07	< 0.001	< 0.001	0.349
Fasting insulin (mU/l) [†]	9.22 ± 0.52	6.94 ± 0.37	10.83 ± 0.46	10.32 ± 0.46	< 0.001	0.004	0.011
1-h insulin (mU/l) [†]	81.0 ± 3.7	64.5 ± 2.8	104.8 ± 3.6	90.5 ± 2.6	< 0.001	< 0.001	0.291
2-h insulin (mU/l) [†]	39.6 ± 2.5	47.9 ± 3.0	60.9 ± 2.5	79.8 ± 3.3	< 0.001	< 0.001	0.432
HOMA IR [†]	1.96 ± 0.12	1.42 ± 0.08	2.33 ± 0.10	2.15 ± 0.08	< 0.001	< 0.001	0.011
Matsuda index [†]	4.08 ± 0.20	5.31 ± 0.25	3.16 ± 0.12	3.43 ± 0.11	< 0.001	< 0.001	0.028
$\Delta I_{0-30}/\Delta G_{0-30}$ [†]	1.13 ± 0.06	1.30 ± 0.07	1.42 ± 0.06	1.71 ± 0.06	< 0.001	< 0.001	0.628
$I/G_{AUC\ 60-120}$ [†]	0.58 ± 0.02	0.56 ± 0.02	0.75 ± 0.02	0.76 ± 0.02	< 0.001	0.924	0.440
$S1Ph_{OGTT}$ [†]	1241 ± 45	1170 ± 40	1451 ± 39	1543 ± 35	< 0.001	0.456	0.046
$S2Ph_{OGTT}$ [†]	331 ± 10	307 ± 9	385 ± 9	397 ± 8	< 0.001	0.777	0.042

Data are *n*, mean ± standard error or rates ± 95% confidence intervals.

[*] Non-adjusted values;

[†] Back-transformed from log transformation.

HOMA IR, homeostasis model assessment of insulin resistance; I_{0-30}/G_{0-30}, insulinogenic index from 0 to 30 min; $I/G_{AUC\ 60-120}$, ratio of area under the insulin curve to area under the glucose curve from 60 to 120 min; $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$, Stumvoll's first phase and second phase insulin release, respectively.

Table 2

Pearson's partial correlations between indices of secretion and with other metabolic variables*

	$\Delta I_{0-30}/\Delta G_{0-30}$†	$I/G_{AUC\ 60-120}$†	$S1Ph_{OGTT}$†	$S2Ph_{OGTT}$†
BMI	0.17	0.37‡	0.36‡	0.39‡
Waist circumference	0.13	0.34‡	0.33‡	0.35‡
Fasting glucose	−0.08	0.05‡	−0.02‡	0.03 §
1-h glucose	−0.38	0.16‡	−0.12‡	−0.06‡
2-h glucose	−0.17	0.15‡	0.01‡	0.05‡
Fasting insulin†	0.24	0.58‡	0.62‡	0.67‡
1-h insulin†	0.32	0.83‡	0.61‡	0.65‡
2-h insulin†	0.24	0.70‡	0.49‡	0.53‡
HOMA IR†	0.30	0.63‡	0.64‡	0.69‡
Matsuda index†	−0.31	−0.78‡	−0.68‡	−0.74‡
$I/G_{AUC\ 60-120}$†	0.51	–	0.74‡	0.77‡
$S1Ph_{OGTT}$†	0.78	0.74§	-	0.99‡
$S2Ph_{OGTT}$†	0.75	0.77	0.99‡	–

*Pearson's partial correlation coefficients were calculated by controlling for age, sex, and ethnic origin;

†log transformed variables.

HOMA IR, homeostasis model assessment of insulin resistance; I_{0-30}/G_{0-30} indicates insulinogenic index from 0 to 30 min; $I/G_{AUC\ 60-120}$, ratio of area under the insulin curve to area under the glucose curve from 60 to 120 min; $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$, Stumvoll first phase and second phase insulin release, respectively. *P*-value for the test of difference in the correlation of each secretory index with individual metabolic variables relative to the respective correlation of $\Delta I_{0-30}/\Delta G_{0-30}$;

‡$P < 0.001$;

§$P < 0.01$

Table 3

Odds ratio of indices of insulin sensitivity and insulin secretion for predicting the 7.8-year incidence of diabetes by multiple logistic regression analysis

	Matsuda index	$\Delta I_{0-30}/\Delta G_{0-30}$	$I/G_{AUC\ 60-120}$	$S1Ph_{OGTT}$	$S2Ph_{OGTT}$	C statistic	*P*
Model 1	0.24 (0.18–0.31)	0.28 (0.22–0.37)	–	–	–	0.875	–
Model 2	0.09 (0.06–0.14)	–	0.21 (0.15–0.28)	–	–	0.858	0.076
Model 3	0.11 (0.07–0.17)	0.41 (0.31–0.54)	0.37 (0.26–0.54)	–	–	0.882	0.044
Model 4*	0.16 (0.10–0.25)	0.43 (0.32–0.58)	0.46 (0.31–0.68)	–	–	0.888	< 0.001
Model 5	0.11 (0.08–0.16)	–	–	0.24 (0.18–0.32)	–	0.873	0.314
Model 6	0.15 (0.10–0.23)	0.50 (0.32–0.79)	–	0.46 (0.28–0.76)	–	0.877	0.792
Model 7	0.10 (0.07–0.14)	–	–	–	0.22 (0.16–0.30)	0.873	0.556
Model 8	0.14 (0.09–0.22)	0.51 (0.33–0.80)	–	–	0.44 (0.25–0.75)	0.877	0.610

Odds ratios expressed for 1 standard deviation unit increase. Age, sex, ethnicity, BMI and family history of diabetes were included as covariates in all eight models.

*Impaired glucose tolerance (IGT) was also added to Model 4 as a covariate.

I_{0-30}/G_{0-30}, insulinogenic index from 0 to 30 min; $I/G_{AUC\ 60-120}$, ratio of area under the insulin curve to area under the glucose curve from 60 to 120 min; and $S1Ph_{OGTT}$ and $S2Ph_{OGTT}$, Stumvoll first phase and second phase insulin release, respectively. *P*-values are for the comparison with Model 1.

Table 4

Comparison of predicted and observed risks of 7.5-year incidence of diabetes in models with and without $I/G_{AUC\ 60–120}$

	Model A plus $I/G_{AUC\ 60–120}$			
(a)	**< 1% yearly risk**	**1–5.9% yearly risk**	**≥ 6% yearly risk**	**% Reclassified**
(a) Model A*				
< 1% yearly risk				
Total, *n*	848	43	0	–
%†	95.2	4.8	–	4.8
Observed yearly risk‡	0.2	1.6	-	-
1–5.9% yearly risk				
Total, n	81	408	23	–
%	15.8	79.7	4.5	20.3
Observed yearly risk	0.7	2.9	10.4	–
≥ 6% yearly risk				
Total, *n*	0	17	75	–
%	–	18.5	81.5	18.5
Observed yearly risk	–	2.4	8.4	–
(b)Model B§	Model B and $I/G_{AUC\ 60–120}$			
< 1% yearly risk				
Total, *n*	907	51	0	–
%†	94.7	5.3	–	5.3
Observed yearly risk‡	0.2	1.3	-	–
1–5.9% yearly risk				
Total, *n*	57	348	15	–
%	13.5	82.9	3.6	17.1
Observed yearly risk	0.7	3.0	8.0	–
≥ 6% yearly risk				
Total, *n*	0	12	105	–
%	–	10.3	81.5	10.3
Observed yearly risk	–	2.4	8.4	–

All estimated and observed risks represent yearly risk of incident diabetes.

*Model A included age, sex, ethnicity, family history of diabetes, BMI, Matsuda index and $\Delta I_{0–30}/\Delta G_{0–30}$ (insulinogenic index from 0 to 30 min) as independent variables.

†Per cent classified in each risk stratum by the model with $I/G_{AUC\ 60–120}$ (ratio of area under the insulin curve to area under the glucose curve from 60 to 120 min).

‡Observed proportion of participants developing diabetes in each category.

§Model B included independent variables of Model A plus impaired glucose tolerance.