What Is the Best Predictor of Future Type 2 Diabetes?

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OBJECTIVE — We sought to assess insulin secretion/insulin resistance index in predicting the risk for future type 2 diabetes

RESEARCH DESIGN AND METHODS — A total of 1,551 nondiabetic subjects from the San Antonio Heart Study received an oral glucose tolerance test (OGTT) with measurement of plasma glucose and insulin concentrations at 0, 30, 60, and 120 min at baseline and after 7–8 years of follow-up. Insulin secretion/insulin resistance index was calculated as the product of Matsuda index and $\Delta I_{0-30}/\Delta G_{0-30}$ or $\Delta I_{0-120}/\Delta G_{0-120}$. The discriminatory power of various prediction models for development of type 2 diabetes was tested with the area under the receiver-operating characteristic (ROC) curve.

RESULTS — Insulin secretion/insulin resistance index (0- to 30- and 0- to 120-min time periods) had the greatest areas under the ROC curve (0.85 and 0.86, respectively), which were significantly greater than the 2-h plasma glucose concentration during the OGTT or the San Antonio Diabetes Prediction Model (SADPM) ($P < 0.001$ and $P < 0.0001$, respectively). A model based on the combination of the SADPM and a modified version of the insulin secretion/insulin resistance index or 1-h plasma glucose concentration had equal power to predict the risk for future type 2 diabetes compared with the insulin secretion/insulin resistance index.

CONCLUSIONS — The insulin secretion/insulin resistance index is useful as a predictor of future development of type 2 diabetes. A model based on the combination of the SADPM and either a modified version of the insulin secretion/insulin resistance index or 1-h plasma glucose concentration can equally predict future type 2 diabetes.

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The worldwide prevalence of type 2 diabetes is increasing at epidemic proportions. In the year 2000, there were 150 million individuals with type 2 diabetes worldwide, and this number is expected to double in the next 25 years (1). This increase in type 2 diabetes prevalence is also associated with increases in both morbidity and mortality (2), despite the decrease in cardiovascular morbidity and mortality in nondiabetic individuals over the same time period (3). For example, in the year 2000 (when compared with 1990), the rate of cardiac events in nondiabetic subjects in New York City declined by 14%, while it increased by 54% in individuals with type 2 diabetes over the same period (2).

Recent clinical trials have demonstrated that, in subjects at high risk for type 2 diabetes, both lifestyle changes and pharmacological intervention can reduce the incidence of type 2 diabetes. A moderate increase in physical activity, accompanied with modest (5–7%) reduction in body weight, reduced the conversion rate of impaired glucose tolerance (IGT) to type 2 diabetes by 58% (4,5). Pharmacological intervention with metformin, troglitazone, and acarbose also have been shown to reduce conversion rate from IGT to diabetes by 31% (3), 75% (6), and 25% (7), respectively. The results of these long-term, prospective studies emphasize the importance of identifying subjects at high risk for type 2 diabetes in order to offer them an intervention program that will prevent/halt their progression to overt diabetes. Demonstration of IGT most commonly has been used to identify subjects at high risk for the development of type 2 diabetes. Indeed, all published studies that have evaluated intervention strategies for preventing type 2 diabetes have recruited subjects with IGT (4–7). However, in prospective epidemiological studies, only 30–40% of subjects with IGT ultimately develop type 2 diabetes (8–10). Furthermore, ~40% of subjects who develop type 2 diabetes have normal glucose tolerance (NGT) at baseline (8). This limits the use of IGT as the sole means to identify subjects at high risk for type 2 diabetes. Such observations have prompted the search for alternative models that more accurately identify subjects at high risk for future type 2 diabetes. A number of models for identifying high-risk subjects have been proposed (11–13). These models are based on risk factors for type 2 diabetes, including age, ethnicity, obesity, lipid profile, blood pressure, and fasting plasma glucose concentration. Although all of these models have value for identifying subjects at risk for future development of type 2 diabetes, their predictive power is similar to or only slightly greater than the 2-h plasma glucose concentration (11–13).

Type 2 diabetes is characterized by defects in both insulin secretion and insulin action (14). Both β-cell dysfunction and insulin resistance can be demonstrated long before overt diabetes is diagnosed, e.g., in subjects with IGT or in NGT subjects with positive family history of type 2 diabetes (14,15). Insulin secretion and insulin resistance can be quantified with the hyperglycemic and euglycemic insulin clamp techniques, respectively (16). However, these techniques are labor intensive and are difficult to apply in clinical practice or in large epidemiological studies. Surrogate measures of insulin secretion and insulin sensitivity have been developed from oral

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Abbreviations: IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; ROC, receiver-operating characteristic; SADPM, San Antonio Diabetes Prediction Model.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

glucose tolerance tests (OGTTs) (17–20). These indexes correlate reasonably well with insulin secretion and insulin sensitivity measured with the hyperglycemic and insulin clamp techniques. Previous epidemiological studies have demonstrated that OGTT-derived measures of insulin resistance and impaired insulin secretion can predict future development of type 2 diabetes (21,22). However, no previous study has examined the ability of an insulin secretion/insulin resistance index to predict future type 2 diabetes and compared this index with other predictive models of type 2 diabetes.

RESEARCH DESIGN AND METHODS

— All subjects were participants of the San Antonio Heart Study (23–25), which is a population-based, epidemiological study of type 2 diabetes and cardiovascular disease. A total of 2,941 Mexican Americans and non-Hispanic whites, aged 25–68 years, were enrolled in phase 2 of the San Antonio Heart Study. We excluded phase 2 participants with overt diabetes at baseline based on World Health Organization criteria (26). We also excluded all phase 1 participants, since in these participants plasma glucose levels were not measured at 30 and 60 min. A total of 2,616 eligible participants, who were free of type 2 diabetes at baseline, completed a 7- to 8-year follow-up examination. Of these 2,616 participants, 1,551 had plasma glucose and insulin measurements at 0, 30, 60, and 120 min during the baseline OGTT and constitute the study population. The study was approved by the institutional review board of University of Texas Health Science Center at San Antonio. All subjects gave written informed consent.

Definition of variables and outcomes

All studies were performed in a mobile clinic following a 12-h overnight fast. A fasting blood specimen was obtained for determination of plasma glucose and serum insulin and lipid concentrations. Following collection of baseline blood sample, subjects ingested 75 g glucose (Orangedex; Custom Laboratories, Baltimore, MD) and blood obtained at 30, 60, and 120 min for determination of plasma glucose and serum insulin concentrations. Plasma glucose and serum lipids were measured with an Abbott Bichromatic Analyzer (South Pasadena, CA). Serum insulin was measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA), which has a relatively high degree of cross-reactivity with proinsulin (~70%). The diagnosis of diabetes was based upon World Health Organization criteria (26): 2-h plasma glucose ≥200 mg/dl or fasting plasma glucose ≥126 mg/dl. Subjects on insulin or oral antihyperglycemic medications also were considered to have diabetes.

Calculations

Areas under the glucose and insulin curves were calculated by the trapezoid rule. Matsuda index of insulin sensitivity (17) was calculated as previously reported. A variation of Matsuda index was calculated by using plasma glucose and insulin concentrations at 30 min during the OGTT in place of mean plasma glucose and insulin concentrations. We refer to this index as the modified Matsuda index. The insulinogenic index was calculated by dividing the increment in serum insulin at 30 min by the increment in plasma glucose at 30 min of OGTT. The insulin secretion/insulin resistance (disposition) index was calculated as the product of insulin secretion measured with ($\Delta I_{0-30}/\Delta G_{0-30}$ or $\Delta I_{0-120}/\Delta G_{0-120}$) and insulin sensitivity index (Matsuda or modified Matsuda indexes). A previously described, multivariate model for predicting future type 2 diabetes, called the San Antonio Diabetes Prediction Model (SADPM) (11) (which includes age, sex, ethnicity, BMI, blood pressure, fasting plasma glucose, triglycerides, and HDL), was also examined, as was the predictive value of the 1-h plasma glucose concentration during the OGTT.

Statistical methods

Variables are presented as means ± SD. The significance of the mean differences was tested with Student's *t* test. Statistical significance was considered at the level of $P < 0.05$. Assessment of the predictive discrimination of the various models was made using the receiver-operating characteristic (ROC) curve by plotting the sensitivity against the corresponding false-positive rate. The area under the ROC curve was used as a measure of how well a continuous variable predicts the development of type 2 diabetes. To examine whether differences between two areas under ROC curves were statistically different, the algorithm developed by DeLong et al. (27) was used. Statistical analyses were performed with the SAS statistical software system (Cary, NC).

RESULTS

— The study included 1,551 subjects: at baseline, 1,257 had normal NGT, 88 had isolated impaired fasting glucose, 154 had isolated IGT, and 52 had both impaired fasting glucose and IGT. A total of 179 subjects progressed to type 2 diabetes after 7–8 years of follow-up; the remaining 1,372 subjects remained free of diabetes at follow-up. Table 1 presents the anthropometric and metabolic characteristics of the two study groups: progressors and nonprogressors. Subjects who progressed to type 2 diabetes were older and had higher BMI, fasting plasma glucose, insulin and triglyceride concentrations, and 2-h plasma glucose and insulin concentrations during OGTT. Indexes of insulin secretion and insulin sensitivity also were lower in subjects who progressed to type 2 diabetes compared with subjects who remained free of diabetes at follow-up.

The area under the ROC curve is presented in Table 2. Similar to previous studies (11), the 2-h plasma glucose concentration had an area under the ROC curve of 0.79 and was comparable to the area under the ROC curve of the SADPM (0.80). Both the SADPM and 2-h plasma glucose concentration had significantly greater area under the ROC curve (0.80 and 0.79, respectively) compared with fasting plasma glucose concentration (ROC = 0.75, $P < 0.05$).

The insulin secretion/insulin resistance index, calculated either with $\Delta I_{0-30}/\Delta G_{0-30}$ or $\Delta I_{0-120}/\Delta G_{0-120}$ (as a measure of insulin secretion) and with the Matsuda index (as a measure of insulin sensitivity), had the greatest areas under the ROC curve (0.85 and 0.86, respectively), and both were significantly greater than that of 2-h plasma glucose concentration and the SADPM ($P < 0.0001$). Combining the SADPM with the insulin secretion/insulin resistance index did not further improve its predictability (Table 2). The area under the ROC curve for the modified insulin secretion/insulin resistance index measured with the modified (30-min) Matsuda index was 0.83, which is only slightly less than that of the unmodified index. However, the combination of the modified insulin secretion/insulin resistance index with the SADPM had comparable area under the ROC curve (0.86) to the unmodified insulin secretion/insulin resistance index.

Plasma glucose concentration at 1 h during the OGTT had a stronger correlation with insulin secretion, insulin resistance, and insulin secretion/insulin

Table 1—*Clinical, anthropometric, and metabolic characteristics of the study groups*

	Nonprogressors	Progressors	*P*
n	1,372	179	NS
Age (years)	43 ± 11	48 ± 10	NS
Sex (% male)	44	39	NS
BMI (kg/m^2)	27.1 ± 5.0	31.3 ± 5.2	<0.0001
Positive family history (%)	29	48	NS
LDL cholesterol (mg/dl)	123 ± 35	124 ± 35	NS
Triglycerides (mg/dl)	134 ± 90	192 ± 121	<0.0001
HDL cholesterol (mg/dl)	47 ± 13	42 ± 11	<0.0001
Total cholesterol (mg/dl)	196 ± 39	200 ± 38	NS
Fasting glucose (mg/dl)	85 ± 10	95 ± 12	<0.0001
2-h plasma glucose (mg/dl)	100 ± 29	140 ± 36	<0.0001
Fasting insulin (μU/ml)	12 ± 13	22 ± 18	<0.0001
2-h serum insulin (μU/ml)	84 ± 88	156 ± 125	<0.0001
$\Delta G(AUC)_{0-120}$ (mg · dl^{-1} · h^{-1})	65 ± 43	123 ± 44	<0.0001
$\Delta I_{0-120}/\Delta G_{0-120}$	2.9 ± 2.6	2.1 ± 2.2	<0.0001
$\Delta I_{0-30}/\Delta G_{0-30}$	2.4 ± 1.6	1.3 ± 0.9	<0.0001
Matsuda index	5.1 ± 5.4	2.3 ± 2.0	<0.0001
Modified Matsuda index	4.8 ± 5.7	2.6 ± 2.1	<0.0001
$\Delta I_{0-120}/\Delta G_{0-120}$ × Matsuda index	20 ± 14	3.6 ± 3.6	<0.0001
$\Delta I_{0-30}/\Delta G_{0-30}$ × Matsuda index	10.1 ± 12.1	2.5 ± 2.7	<0.0001
$\Delta I_{0-30}/\Delta G_{0-30}$ × modified Matsuda index	9.1 ± 10.7	2.8 ± 2.3	<0.0001

Data are means ± SD unless otherwise indicated. AUC, area under the curve; NS, not significant.

resistance index compared with the 2-h plasma glucose concentration (Table 3). Therefore, we examined the ability of the 1-h plasma glucose concentration to predict future type 2 diabetes. The area under the ROC curve for 1-h plasma glucose (0.84) (Table 2) was significantly greater than the area under the ROC curve for the 2-h plasma glucose concentration and the SADPM (both $P = 0.01$). Addition of the 1-h plasma glucose concentration to the SADPM significantly improved its predictability at a level similar to that of insulin secretion/insulin resistance index.

When a cut point for continuous variables was used as a threshold for predicting future type 2 diabetes, IGT (2-h plasma glucose = 140–199 mg/dl) had the greatest specificity (92%) but the sensitivity was only 51%. The use of plasma glucose concentration = 155 mg/dl at 60 min during the OGTT as a cut point had 75% sensitivity and 79% specificity. Both the 0- to 30-min and 0- to 120-min insulin secretion/insulin resistance indexes had greater sensitivity compared with IGT, although the specificity declined slightly (Table 2).

CONCLUSIONS

Clinical trails consistently have demonstrated that lifestyle intervention in subjects with IGT markedly reduces the risk for conversion to type 2 diabetes. However, the identification of subjects with IGT requires that an OGTT be performed, and the time required (2-h) to complete the OGTT has limited its widespread use in clinical practice. Moreover, although the present results demonstrate that the OGTT diagnosis of IGT has high specificity (92%) in predicting which subjects are at high risk for developing type 2 diabetes, it has much lower sensitivity (51%). Thus, if one relies exclusively on the OGTT diagnosis of IGT for identifying high-risk individuals, about half of those who ultimately convert to type 2 diabetes would not have been identified.

Our results demonstrate that the insulin secretion/insulin resistance index is the best predictor of future type 2 diabetes (Table 2). When it is calculated with either $\Delta I_{0-30}/\Delta G_{0-30}$ or $\Delta I_{0-120}/\Delta G_{0-120}$ (as the measure of insulin secretion) and the Matsuda index (as the measure of insulin resistance), it has the greatest area under the ROC curve (0.85 and 0.86, respectively). Combining the SADPM predictive model (11) with the insulin secretion/insulin resistance index does not further enhance its predictability. Of note, in previous studies indexes of insulin secretion and insulin resistance were found to be significant independent predictors for future type 2 diabetes (21,22). Although they were not compared with the 2-h plasma glucose concentration, all of the indexes that were tested had an area under the ROC curve <0.8 (21). No previous study has assessed the ability of any insulin secretion/insulin resistance index to predict future type 2 diabetes. One limitation in using the insulin secretion/insulin resistance index for predicting future type 2 diabetes is the need to measure the plasma glucose and insulin concentrations every 30 min during the OGTT. This limitation can be overcome by using the modified insulin secretion/insulin resistance index. Although the

Table 2—*Area under the ROC curve for various predictive models for future development of type 2 diabetes*

Parameter	ROC	*P* vs. G_{120}	ROC combined model*	Cutoff	Sensitivity	Specificity
Fasting plasma glucose	0.75	0.05				
Plasma glucose at 30 min	0.77	0.24				
Plasma glucose at 60 min	0.84	0.01	0.86†	155	0.75	0.79
Plasma glucose at 120 min	0.79			140	0.51	0.92
SADPM	0.80					
Glucose (AUC) 0–120 min	0.83	0.06	0.87†		0.83	0.71
$\Delta I_{0-120}/\Delta G_{0-120}$ × Matsuda index	0.86	<0.0001	0.86†	4.5	0.82	0.76
$\Delta I_{0-30}/\Delta G_{0-30}$ × Matsuda index	0.85	0.005	0.87†	3.1	0.83	0.77
$\Delta I_{0-30}/\Delta G_{0-30}$ × modified Matsuda index	0.83	0.1	0.86†	3.5	0.82	0.71

*The combined model is comprised of the combination of each parameter with SADPM. †$P < 0.0001$ vs. SADPM; P = NS vs. ROC. AUC, area under the curve.

Table 3—*Pearson's correlation coefficients between plasma glucose concentration at 60 and 120 min during the OGTT versus indexes of insulin secretion and insulin resistance*

Parameter	Glucose at 60 min	*P*	Glucose at 120 min	*P*
Fasting plasma glucose	0.5	<0.0001	0.35	<0.0001
Plasma glucose at 120 min	0.6	<0.0001	—	—
Matsuda index	−0.44	<0.0001	−0.39	<0.0001
$\Delta I_{0-30}/\Delta G_{0-30}$	−0.36	<0.0001	−0.14	0.07
ΔGlucose (AUC) 0–120 min	0.91	<0.0001	0.73	<0.0001
$\Delta I_{0-120}/\Delta G_{0-120}$ × Matsuda index	−0.44	<0.0001	−0.34	<0.0001
$\Delta I_{0-30}/\Delta G_{0-30}$ × Matsuda index	−0.53	<0.0001	−0.36	<0.0001

AUC, area under the curve.

area under the ROC curve (0.83) for the modified insulin secretion/insulin resistance index calculated with $\Delta I_{0-30}/\Delta G_{0-30}$ and a modified version of the Matsuda index (calculated with plasma glucose and insulin concentrations at fasting and 30 min) is slightly lower than that of the unmodified index, combination of the modified insulin secretion/insulin resistance index and SADPM has an area under its ROC curve that is comparable to that of the unmodified index in predicting future diabetes. Use of this model in clinical practice is more convenient than the OGTT diagnosis of IGT because it requires the measurement of plasma glucose and insulin concentrations only at baseline (fasting) and 30 min following the glucose load.

Simply measuring the plasma glucose concentration at 1 h during the OGTT also is a good predictor for future type 2 diabetes. It has a greater area under the ROC curve compared with the 2-h plasma glucose concentration, and, when combined with the SADPM, its area under the ROC curve is comparable with the insulin secretion/insulin resistance index. Furthermore, if one uses a cut point of 155 mg/dl for the 1-h plasma glucose concentration, this has 50% greater sensitivity in predicting future type 2 diabetes compared with the OGTT diagnosis of IGT with only a modest (~15%) decline in specificity. Because the glucose assay is universally standardized, the combination of 1-h plasma glucose concentration and the SADPM provides an additional method for predicting future type 2 diabetes. This combination is more accurate than 2-h plasma glucose concentration during the OGTT and more convenient than the diagnosis of IGT because the plasma glucose concentration is measured at 1 h instead of after 2 h.

Prediction models can serve one of two purposes: *1*) identification of high-risk target populations for clinical and public health intervention and 2) elucidating the pathogenesis of the disease. The models presented in this study reflect primarily the second goal. They demonstrate that a prediction model based on the pathophysiology of the disease performs superiorly to other clinical models in predicting the risk of future type 2 diabetes. With respect to the first goal, one must weigh the greater accuracy of the presented models against the added cost, both in terms of dollars and inconvenience associated with performing the OGTT, which the SADPM does not require. Depending on the circumstances, one or another approach may be preferred.

In summary, the present results demonstrate that the insulin secretion/insulin resistance index derived from the OGTT provides a superior method for predicting future development of type 2 diabetes compared with the diagnosis of IGT based on the 2-h plasma glucose concentration. The combination of the SADPM with the 1-h plasma glucose concentration and a modified version of the insulin sensitivity/insulin resistance index provides alternative predictive models with similar precision and does not require the measurement of plasma glucose concentration 2 h after ingestion of the glucose load.

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