The BIGTT Test

A novel test for simultaneous measurement of pancreatic β-cell function, insulin sensitivity, and glucose tolerance

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OBJECTIVE — Insulin resistance and impaired β-cell function are key elements in the pathogenesis of type 2 diabetes. We aimed to develop valid algorithms for estimation of the insulin sensitivity index (S_I) and acute insulin response (AIR) derived from simple and cheap physiological measurements that could be used in large-scale metabolic, genetic, and epidemiological studies.

RESEARCH DESIGN AND METHODS — For our purpose, data from an oral glucose tolerance test (OGTT) (18 samples during 240 min) and a tolbutamide-modified intravenous glucose tolerance test (IVGTT) (33 samples during 180 min) from 258 individuals with fasting plasma glucose <7 mmol/l and 2-h plasma glucose <7.8 mmol/l were used for model development and internal validation. Data from an additional 28 individuals were used for external validation. Bergman's minimal model was used to calculate S_I, and the trapezoidal method was used to calculate $AIR_{0-8\ min}$. Multiple linear regression was applied to derive predictive equations of $\log(S_I)$ and $\log(AIR_{0-8\ min})$ using data on sex, BMI, plasma glucose, and serum insulin levels obtained during the OGTT.

RESULTS — We demonstrate that it is possible to obtain estimates of S_I (BIGTT-S_I) and AIR (BIGTT-AIR) that are highly correlated to IVGTT-derived values of S_I ($R^2 = 0.77$) and AIR ($R^2 = 0.54$). In the two validation datasets we obtained similar results.

CONCLUSIONS — Data from OGTTs can provide accurate measures of insulin sensitivity and β-cell function, which can be used in large scale metabolic, genetic, and epidemiological studies.

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The maintenance of normal glucose homeostasis involves the simultaneous and coordinated roles of insulin release from the pancreatic β-cells and insulin action on peripheral tissues, primarily muscle (1,2). For estimation of whole-body insulin sensitivity, the euglycemic-hyperinsulinemic clamp is considered the "gold standard" (3). The assessment of the insulin sensitivity index (S_I) by the minimal model for the intravenous glucose tolerance test (IVGTT) has also been used in numerous studies (4), because the method has the advantage of providing simultaneous information on the S_I and acute insulin response (AIR). Both methods are considered to provide exact and, among individuals with normal glucose tolerance, comparable measurements of insulin sensitivity (5). However, because these methods are time consuming and expensive and cannot be performed on the same day as an oral glucose tolerance test (OGTT), neither is suitable for large-scale studies.

In the present study, we examine nondiabetic individuals without impaired glucose tolerance (IGT) to derive equations that are more accurate than those currently available for the S_I and the AIR from an OGTT (1,6–12). We have used detailed information from both plasma glucose and serum insulin levels during an extended and frequently sampled OGTT combined with information on anthropometric measures and sex to generate equations and data from a frequently sampled IVGTT performed in the same individuals as reference. The approach is empirical and data driven, with multiple regression statistics being applied to the physiological data obtained.

RESEARCH DESIGN AND METHODS

Individuals for model development and internal validation

OGTT data from 258 individuals with fasting plasma glucose <7.0 mmol/l and 2-h plasma glucose <7.8 mmol/l (nondiabetic without IGT) were used to develop (75% of the data) and validate (25% of the data) models. All participants were from 1 of 60 families as described previously (13). The performance of the model was further examined in 28 individuals with IGT identified in the same 60 families. Before participation in the study, all individuals provided informed consent. The study was approved by the Ethical Committee of Copenhagen and was in accordance with the principles of the Declaration of Helsinki.

OGTT

All individuals underwent a standardized and extended 75-g frequently sampled OGTT. After a 12-h overnight fast, venous blood samples were drawn in triplicate at

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Abbreviations: AIR, acute insulin response; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; RCPH, Research Centre for Prevention and Health.

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

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−10, −5, and 0 min before the OGTT and at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 140, 160, 180, 210, and 240 min from the start of the glucose load for analysis of plasma glucose and serum insulin levels. The plasma glucose concentration was analyzed by a glucose oxidase method (Granutest; Merck, Darmstadt, Germany). Serum insulin was determined by enzyme-linked immunoadsorbent assay with a narrow specificity excluding des(31,32)-proinsulin and intact proinsulin (DAKO Diagnostics, Ely, U.K.) (14).

IVGTT

All individuals underwent a 33-point tolbutamide-modified, frequently sampled IVGTT (13) within 1 week after the OGTT examination except for a few individuals who underwent an IVGTT within 4 weeks. The S_I was calculated using the Bergman MINMOD computer program (15). The glucose-induced serum $AIR_{insulin\ 0-8\ min}$ was calculated as the incremental areas under the curves from 0 to 8 min.

Individuals for external validation

Twenty-eight nondiabetic individuals without IGT, randomly chosen from participants in a population-based study at the Research Centre for Prevention and Health (RCPH) of 695 individuals born in 1936 (16), were examined by both an OGTT and an IVGTT. An extended 75-g OGTT was performed after a 10-h overnight fast. Blood samples were drawn in duplicate between 7:45 and 10:00 A.M. before the oral glucose load, i.e., at −5 and 0 min and at 15, 30, 45, 60, 90, 120, and 180 min after the glucose load. Plasma glucose levels were analyzed at the RCPH using a glucose oxidase method (17). Serum insulin was analyzed at Steno Diabetes Center (14). The IVGTT was performed at Steno Diabetes Center by the protocol described above (13).

Anthropometric measurements

Body weight (with light clothing) was measured to the nearest 0.1 kg and height (without shoes) was estimated to the nearest 0.5 cm. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference (to the nearest centimeter, individuals without clothes) was measured midway between the lowest rib and the iliac crest on standing subjects. Hip circumference (to the nearest centimeter with individuals in underwear) was measured over the widest part of the gluteal region. Fat mass was measured using a bioelectrical impedance method (18).

Statistical methods

An empirical data-driven approach was chosen, using multiple linear regression to derive predictive equations of log(S_I) and log(AIR), i.e., the natural logarithm. Demographic data and glucose and insulin concentrations during the OGTT were used as independent variables in the analysis. To adjust for within-family correlation, a random family factor was added to the models. An a priori analysis strategy was formulated to ensure efficient exploitation of the data. The models were based on untransformed and transformed glucose and insulin results (square and reciprocal transformation) and standardized areas under the concentration curves for plasma glucose and serum insulin, defined as the area under the curve, above baseline from time 0 to time t minutes divided by t. The demographic factors included age, sex, height, body weight, waist circumference, hip circumference, fat mass, BMI, waist-to-hip ratio, and fat mass-to-body weight ratio.

Of the total data, ~75% were randomized (stratified according to age and missing data status) to an estimation sample used for predicting log(S_I) and log(AIR). The remaining 25% of the data were considered as an internal validation sample for assessment of the accuracy of the predictive equations, i.e., a cross validation. Furthermore, external validation was provided by the application of the predictive models to the data from the RCPH.

A combination of backwards elimination and forward selection was chosen in the modeling phase to handle the large number of variables in each model. A model was initially based on plasma glucose and serum insulin levels at 0, 30, 60, 90, 120, and 180 min as regression variables to describe the established indexes of insulin sensitivity and β-cell function. Depending on which of these variables was statistically significant at a 10% significance level, values at adjacent time points were added sequentially to the model. We have thus used plasma glucose and serum insulin responses from several time points during the OGTT to generate the optimal equations for OGTT-derived indexes of insulin sensitivity (BIGTT-$S_{I|full}$) and β-cell function (BIGTT-AIR_{full}). Also, we generated and tested simple indexes of S_I and AIR using time points that are routinely measured in most metabolic, genetic, and epidemiological studies, i.e., at 0, 30, and 120 min (BIGTT-$S_{I|0\text{-}30\text{-}120}$ and BIGTT-$AIR_{0\text{-}30\text{-}120}$), and 0, 60, and 120 min (BIGTT-$S_{I|0\text{-}60\text{-}120}$ and BIGTT-$AIR_{0\text{-}60\text{-}120}$), respectively.

Evaluations and comparisons between models were based on the residual SD and the correlation coefficient (R^2) obtained from the regressions. R^2 describes the degree of variation explained by the model relative to the total variation in the population subjected to analysis. Because R^2 is population dependent, it can only be used for comparisons of models within a dataset, not between datasets. However, the SD is comparable between models applied to various datasets, as the SD on the log scale corresponds approximately to the coefficient of variation of the predicted S_I and AIR on the original scale.

Calculations of insulin sensitivity and acute insulin response using previously published models

Formulas from previously published models were applied to the present datasets to compare the accuracy of the different models (Table 3). As previously described models were not based on log-transformed measures of insulin sensitivity and β-cell function, the accuracy has been assessed after performance of an adjustment based on a regression analysis of the log-transformed result of each formula, measuring concordance with the log(S_I) and log(AIR) estimating an intercept based on the estimation dataset. Thus, the risk of performing an unfair comparison with the BIGTT models is eliminated, because additional corrections to the data are obtained by the adjustment.

RESULTS — Characteristics of participants are given in Table 1. Table 2 shows the predictive equations that were generated for calculations of BIGTT-S_I and BIGTT-AIR. Estimates of S_I (BIGTT-$S_{I|full}$) and AIR (BIGTT-AIR_{full}) were highly correlated to IVGTT-derived values of S_I (R^2 = 0.77) and AIR (R^2 = 0.54) (Table 3).

Each of the OGTT-derived estimates of S_I was compared to estimates of S_I obtained in the internal and external validation dataset as well as to estimates of insulin sensitivity using the fasting insulin level, the homeostasis model assessment (HOMA), and four other previously published models (Table 3). On the basis of the SD of the estimates, both the full model (BIGTT-$S_{I|full}$) and the two more simple models (BIGTT-$S_{I|0\text{-}30\text{-}120}$ and BIGTT-$S_{I|0\text{-}60\text{-}120}$) for estimation of S_I had an ~30% higher accuracy than two

Table 1—*Clinical and biochemical data for 258 nondiabetic individuals without IGT used for model development and internal validation and for 28 nondiabetic individuals without IGT for external validation*

	Model development and internal validation	External validation
n (men/women)	110/148	16/12
Age (years)	42 ± 12	61 ± 0.2
BMI (kg/m^2)	26.0 ± 4.5	25.1 ± 2.6
Plasma glucose (mmol/l)		
t = 0 min	5.1 ± 0.7	5.2 ± 0.5
t = 30 min	8.1 ± 1.5	7.8 ± 1.4
t = 60 min	7.9 ± 2.0	7.5 ± 2.0
t = 120 min	5.7 ± 1.2	5.0 ± 1.3
Serum insulin (pmol/l)		
t = 0 min	40 ± 26	32 ± 13
t = 30 min	316 ± 198	228 ± 125
t = 60 min	371 ± 232	260 ± 132
t = 120 min	214 ± 182	164 ± 121
S_I [10^{-5} · (min · pmol/l)$^{-1}$]	10.6 ± 6.2	12.7 ± 6.9
$AIR_{0–8\ min}$ (min · pmol/l)	2,478 ± 1,762	1,523 ± 925

Values are means ± SD.

widely used simple indexes of insulin sensitivity, i.e., fasting insulin and HOMA (Table 3). The OGTT-derived estimates of S_I were almost similar in the two validation datasets (Table 3). The relationship between S_I obtained from the IVGTT and BIGTT-$S_{I|0\text{-}60\text{-}120}$ is presented in Fig. 1*A*, which shows a high degree of correlation at all levels of insulin sensitivity. A similar correlation at all levels of insulin sensitivity is seen by applying the optimal model (BIGTT-$S_{I|full}$) as well as the BIGTT-$S_{I|0\text{-}30\text{-}120}$ (data not shown).

The SD and R^2 for various indexes of β-cell function are also shown in Table 3. The novel BIGTT-AIR methods are about 20–30% more accurate than three currently used models for estimation of β-cell function, and the estimates were very similar in the two validation datasets (Table 3). The relationship between β-cell function estimated by the IVGTT and by the BIGTT-$AIR_{0\text{-}60\text{-}120}$ is shown in Fig. 1*B*.

For subjects with IGT, the BIGTT models for the estimation of indexes of insulin sensitivity and β-cell function were less accurate than when they were applied to data from nondiabetic individuals without IGT (see Table 1 of the online appendix available at http://dx.doi.org/10.2337/dc06-1240). This was a general observation for all applied models. However, the Matsuda, Cederholm, and Belfiori indexes did seem to capture the insulin sensitivity for subjects with IGT in a more satisfactory manner than the BIGTT model. Regarding the indexes of β-cell function, the BIGTT model was more accurate than the alternative models (see Table 1 of the online appendix).

CONCLUSIONS — We present novel and validated models for calculation of S_I and AIR with data available from an OGTT. The models are developed for accurate measurement of S_I and AIR in nondiabetic individuals without IGT. The plasma glucose level obtained at 120 min after the ingestion of the glucose load identifies individuals for whom the method is applicable and at the same time identifies individuals having IGT or overt diabetes. Patients with type 2 diabetes and IGT are characterized by various degrees of abnormalities in both insulin action and insulin secretion (19), and it is therefore unlikely that models for mea-

Table 2—*OGTT-derived models for calculations of S_I and AIR in nondiabetic individuals without IGT*

Name of model	Blood sampling time points for measurements of plasma glucose and serum insulin during an OGTT	Equation
BIGTT-$S_{I\|0\text{-}30\text{-}120}$	0, 30, and 120 min	$\exp[4.90 - (0.00402 \cdot I_0) - (0.000556 \cdot I_{30}) - (0.00127 \cdot I_{120}) - (0.152 \cdot G_0) - (0.00871 \cdot G_{30}) - (0.0373 \cdot G_{120}) - (0.145 \cdot \text{sex}) - (0.0376 \cdot \text{BMI})]$
BIGTT-$S_{I\|0\text{-}60\text{-}120}$	0, 60, and 120 min	$\exp[4.62 - (0.00385 \cdot I_0) - (0.000917 \cdot I_{60}) - (0.000760 \cdot I_{120}) - (0.0551 \cdot G_0) - (0.0178 \cdot G_{60}) - (0.0524 \cdot G_{120}) - (0.144 \cdot \text{sex}) - (0.0380 \cdot \text{BMI})]$
BIGTT-$S_{I\|full}$	0, 30, 60, 105, 180, and 240 min	$\exp[4.39 - (0.000287 \cdot I_0) - (0.000424 \cdot I_{30}) - (0.000848 \cdot I_{60}) - (0.000691 \cdot I_{105}) + (0.000144 \cdot I_{180}) - (0.00282 \cdot I_{240}) - (0.161 \cdot G_0) + (0.0357 \cdot G_{30}) - (0.0130 \cdot G_{60}) - (0.0416 \cdot G_{105}) - (0.106 \cdot G_{180}) + (0.169 \cdot G_{240}) - (0.177 \cdot \text{sex}) - (0.031 \cdot \text{BMI})]$
BIGTT-$AIR_{0\text{-}30\text{-}120}$	0, 30, and 120 min	$\exp[8.20 + (0.00178 \cdot I_0) + (0.00168 \cdot I_{30}) - (0.000383 \cdot I_{120}) - (0.314 \cdot G_0) - (0.109 \cdot G_{30}) + (0.0781 \cdot G_{120}) + (0.180 \cdot \text{sex}) + (0.032 \cdot \text{BMI})]$
BIGTT-$AIR_{0\text{-}60\text{-}120}$	0, 60, and 120 min	$\exp[8.19 + (0.00339 \cdot I_0) + (0.00152 \cdot I_{60}) - (0.000959 \cdot I_{120}) - (0.389 \cdot G_0) - (0.142 \cdot G_{60}) + (0.164 \cdot G_{120}) + (0.256 \cdot \text{sex}) + (0.038 \cdot \text{BMI})]$
BIGTT-AIR_{full}	0, 10, 50, and 140 min	$\exp[7.91 + (0.000898 \cdot I_0) + (0.00163 \cdot I_{10}) + (0.00127 \cdot I_{50}) - (0.000966 \cdot I_{140}) - (0.0323 \cdot G_0) - (0.0377 \cdot G_{10}) - (0.0985 \cdot G_{50}) + (0.143 \cdot G_{140}) + (0.289 \cdot \text{sex}) + (0.036 \cdot \text{BMI})]$

Sex (female = 0, male = 1); I_t is serum insulin (picomoles per liter); G_t is plasma glucose (millimoles per liter) at time t min; exp[ ] denotes the exponential function; 0 min is calculated as the mean of values obtained at −10, −5, and 0 min.

Table 3—*SD and* R^2 *for various indices of the* S_I *compared with the* S_I *as estimated from an IVGTT and indices of* β*-cell function compared with AIR as calculated from an IVGTT

Model	Estimation dataset	Internal validation dataset	External validation dataset
Estimates of S_I			
BIGTT-$S_{I\|full}$	0.30 (0.77)	0.36	ND
BIGTT-$S_{I\|0\text{-}30\text{-}120}$	0.36 (0.69)	0.38	0.38
BIGTT-$S_{I\|0\text{-}60\text{-}120}$	0.34 (0.71)	0.35	0.39
Fasting serum insulin	0.46 (0.49)	0.53	0.45
HOMA	0.45 (0.50)	0.54	0.45
Matsuda	0.38 (0.65)	0.41	0.43
Cederholm	0.47 (0.45)	0.49	0.47
Belfiori	0.41 (0.58)	0.41	0.41
Stumvoll	0.45 (0.51)	0.57	0.42
Indices of β-cell function			
BIGTT-AIR_{full}	0.42 (0.54)	0.45	ND
BIGTT-$AIR_{0\text{-}30\text{-}120}$	0.46 (0.47)	0.44	0.40
BIGTT-$AIR_{0\text{-}60\text{-}120}$	0.45 (0.47)	0.46	0.39
Modified Kadowaki model	0.59 (0.14)	0.63	0.55
HOMA	0.54 (0.25)	0.58	0.59
Stumvoll	0.55 (0.27)	0.62	0.64

Data are SD (R^2) or SD. In the various formulas below, plasma glucose is entered as millimoles per liter and serum insulin as picomoles per liter, unless otherwise stated. G_t and I_t denote plasma glucose and serum insulin concentrations, respectively, at a given time (t in minutes) after ingestion of the oral load. G_{mean} and I_{mean} are the means of plasma glucose and serum insulin concentrations during the sampling periods in question. Models of insulin sensitivity are as follows. *HOMA model*. Only fasting values of plasma glucose and serum insulin are used (9): $I_0/(22.5e^{-\ln G_0})$. *Matsuda model*. Plasma glucose and serum insulin levels are measured at $t = -30, -15, 0, 30, 60, 90$, and 120 min during the OGTT. Values of plasma glucose and serum insulin are entered in the formula as milligrams per deciliter and milliunits per liter, respectively (8): 10,000/square root of $(G_0 \cdot I_0 \cdot G_{mean} \cdot I_{mean})$. In the present study plasma glucose and serum insulin levels measured at $t = -10$ and $t = -5$ were used instead of $t = -30$ and $t = -15$, respectively. *Cederholm model*. Plasma glucose and serum insulin levels are measured at $t = 0$, 30, 60, and 120 min during the OGTT (11): [75/120 + $(G_0 - G_{120})$ 1.15 · 180 · 0.19 · body weight)/(120 · log(I_{mean}) · G_{mean}). *Belfiori model*. Plasma glucose and serum insulin levels are measured at 0, 60, and 120 min (7): $2/[(I_{mean\text{-}person}/I_{mean\text{-}population}) \cdot (G_{mean\text{-}person}/G_{mean\text{-}population})] + 1$. *Stumvoll model*. Plasma glucose and serum insulin levels are measured at $t = 0$, 90, and 120 min during the OGTT (10): $18.8 - 0.271 \cdot \text{BMI} - 0.0052 \cdot I_{120} - 0.27 \cdot G_{90}$. Models of β-cell function are as follows. *HOMA model*. Only fasting values of plasma glucose and serum insulin are used (9): $20 \cdot I_0/(G_0 - 3.5)$. *Modified Kadowaki model*. Plasma glucose and serum insulin levels are measured at 0 and 30 min (12,22): $(I_{30} - I_0)/G_{30}$. *Stumvoll model*. Plasma glucose and serum insulin levels are measured at $t = 0$ and 30 min during the OGTT (10): $1{,}283 + 1.829 \cdot I_{30} - 138.7 \cdot G_{30} + 3.772 \cdot G_0$. ND, not determined.

surements of insulin sensitivity and β-cell function derived from an OGTT could be accurate throughout the whole spectrum of glucose tolerance (20). As expected, our model did not work as well in individuals with IGT (see Table 1 of the online appendix). If detailed information on β-cell function and/or insulin sensitivity is essential in these individuals, other methods have to be used in addition to the OGTT. All three BIGTT-S_I models were highly positively correlated (R^2 = 0.69–0.77) to the S_I derived from an IVGTT. This was the case for both the estimation dataset and the validation datasets. As correlation coefficients should not be used for comparisons between studies, we also report the residual SD of log(S_I) for the various models derived from the present dataset. We find that all of our three models provide more accurate estimates of insulin sensitivity than various previously published methods (7–12). The higher accuracy of the present models might be due to *1*) the fact that the models were developed using detailed data from a relatively large study population (n = 194), *2*) only data from nondiabetic individuals without IGT were used for model development to avoid the confounding effect of overt hyperglycemia on estimates of insulin secretion and action, and *3*) the fact that information on sex and BMI were included. It is noteworthy that for log(S_I) the estimated parameters for sex and BMI show a high degree of consistency among the different models, indicating that adjustment for these factors is indeed relevant. However, adding information about sex and BMI to previously used indexes did not improve their accuracy.

In the present study we have chosen to use insulin sensitivity estimates from a frequently sampled IVGTT as reference for the BIGTT-S_I models. Most other published OGTT-derived models for estimation of insulin sensitivity are developed on the basis of data from euglycemic-hyperinsulinemic clamp studies. We believe, however, that our models provide an estimate of insulin sensitivity that could be compared with clamp data, as previous reports have shown a strong positive correlation between S_I obtained from the frequently sampled IVGTT and S_I obtained from the euglycemic-hyperinsulinemic clamp in normoglycemic individuals (5,21).

The models derived from OGTT data for measurement of β-cell function were developed with the $AIR_{0-8\ min}$ response from the IVGTT, which is the gold standard, as reference. The models are highly accurate compared with other available methods using OGTT data for calculation of insulin secretion (Table 3) (9,12,22–26). Both our models and other models for measurement of β-cell function were less accurate when applied to individuals with IGT, but the BIGTT model was still more accurate than the alternative models (see Table 1 of the online appendix). Adding information on sex, height, and weight to previously used indexes did not improve their accuracy.

In contrast to anthropometric variables, which are reproducible among laboratories, assay characteristics for measurement of serum insulin such as linearity, recovery, accuracy, precision, and cross-reactivity to proinsulin and its primary conversion intermediates vary among laboratories (27). In the present model we have used an insulin assay with no cross-reactivity to proinsulin and its primary conversion intermediates (14). Whether our model is valid when serum insulin levels are analyzed by other assays remains to be studied.

In summary, we have developed and validated novel models for assessment of OGTT-derived estimates of S_I and AIR. Information on sex and BMI combined with analysis of plasma glucose and serum insulin levels in the fasting state and up to eight time points during 4 h (full models) provides indexes for S_I and AIR that are highly correlated to indexes obtained from a frequently sampled IVGTT. Furthermore, we have validated more simple OGTT-based models that can be used to predict estimates of S_I and AIR, incorporating information on sex, BMI,

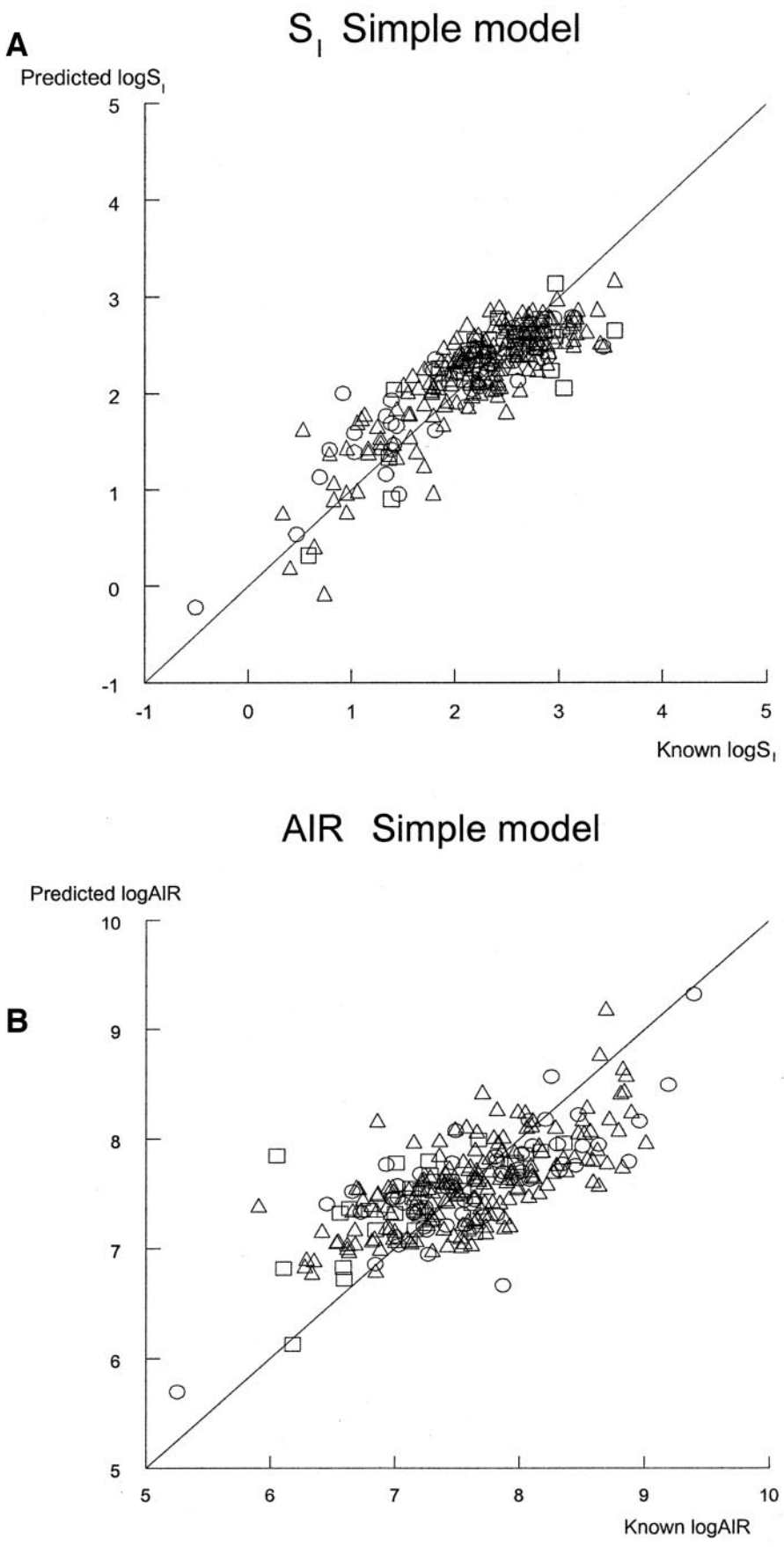

Figure 1—A*: Relationship between* S_I *obtained from an IVGTT [known log*(S_I)*] and* S_I *obtained from OGTT-based data from plasma glucose and serum insulin levels at* t = *0, 60, and 120 min; sex; and BMI [predicted log (BIGTT-*$S_{I|0\text{-}60\text{-}120}$*)]. Triangles depict data from the estimation sample; circles and squares depict data from the internal and external validation samples, respectively*. B*: Relationship between serum AIR during 0–8 min obtained from an IVGTT [known log(AIR)] and AIR obtained from OGTT-based data using information from plasma glucose and serum insulin levels at* t = *0, 60, and 120 min; sex; and BMI [predicted log(BIGTT-*$AIR_{0\text{-}60\text{-}120}$*)]. Triangles depict data from the estimation sample; circles and squares depict data from the internal and external validation samples, respectively*.

and measurement of plasma glucose and serum insulin levels at 0, 30, 60, and 120 min. The models are designed for nondiabetic individuals without IGT; glucose tolerance is also being estimated from the OGTT. Because of the simplicity of these models, they can be implemented in large scale metabolic, genetic, and epidemiological studies.

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