original article

# Levels of the first-phase insulin secretion deficiency as a predictor for type 2 diabetes onset by using clinical-metabolic models

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**AIMS:** Type 2 diabetes mellitus (T2DM) is characterized by both decreased insulin sensitivity and impaired insulin secretion. The 2 phases of insulin secretion are the first-phase insulin secretion (1st ISEC) and the second-phase insulin secretion. In this study, we tried to build clinical-metabolic models to predict the 1st ISEC deficiency (ISEC-D) in non-diabetic subjects so that early intervention could be started.

**DESIGN AND SETTINGS:** A cross-sectional study was conducted in the clinical research department of a hospital in Taiwan from 2010 to 2011.

**METHODS:** A total of 89 subjects without diabetes were enrolled in the study, including 49 with normal glucose tolerance and 40 pre-diabetes. A frequently sampled intravenous glucose tolerance test was done to determine insulin sensitivity and acute insulin response after the glucose load, which is regarded as the 1st ISEC. Subjects with the lowest tertile of the 1st ISEC were defined as ISEC-D. From the simplest to the most complex, 3 models were build: Model 0: fasting plasma glucose (FPG); Model 1: FPG + body mass index (BMI) + High-density lipoprotein cholesterol (HDL-C); Model 2: Model 1+ fasting plasma insulin (FPI). The area under the receiver-operating characteristic curve (aROC curve) was used to determine the predictive power among these models. An optimal cut-off value was also determined.

**RESULTS:** Among metabolic syndrome (MetS) components (FPG, BMI, and HDL-C), FPG had the greatest aROC curve (70.9%). Moreover, the aROC curves of Models 1 and 2 were all significantly greater than that of FPG (80.4% and 82.3%, respectively). Their aROC curves were also greater than that of the homeostasis model assessment β-cell (HOMA-β) function, which is the most commonly used method to evaluate β–cell function.

**CONCLUSION:** By using only MetS components, ISEC-D could be predicted with an acceptable sensitivity of 84.0% and a specificity of 74.0%. However, after adding FPI into the Model, the predictive power of Model 2 did not increase. These model-derived MetS components could be widely used in clinical settings and early detection of non-diabetic subjects with high risk for T2DM.

It is well known that type 2 diabetes mellitus (T2DM) is a heterogeneous disease and mainly characterized by both impaired insulin sensitivity and insulin secretion.[1] For subjects prone to diabetes, the plasma glucose is usually maintained within its normal range before middle age until the compensation of the β-cell to insulin resistance (IR) fails. Based on the findings of the United Kingdom Prospective Diabetes Study, β-cell function has already decreased more than 50% 10 years before the time when diabetes was diagnosed.[2] Other than this, Fukushima et al and our group also showed that in Asians, the deterioration of β-cell function might play a more important role than impaired insulin sensitivity in the development of T2DM.[3,4]

Cerasi et al was the first one to demonstrate the existence of biphasic insulin secretion in response to a square-wave glucose infusion.[5] Normally, after exposure to a prompt elevation in plasma glucose levels, the first-phase insulin secretion (1st ISEC) is secreted by β-cells within 10 minutes and followed by a sustained second-phase insulin secretion.[6] Caumo et al showed

that in subjects with a greater peak of the 1st ISEC, normal glucose will be maintained longer.[6] This observation is in accordance with the previous results that, in the early stage of T2DM, the 1st ISEC already becomes exhausted or even completely disappears.[7,8] From these 2 studies we can draw the conclusion that the 1st ISEC could be regarded as the most sensitive marker for the impaired glucose tolerance in "clinically normal" individuals before the fully developed diabetes.[9,10]

The metabolic syndrome (MetS) was first proposed in the hope to early detect subjects under high risk for cardiovascular diseases and T2DM.[11,12] After its publication, Hanley et al showed that IR is the core of this syndrome, and each MetS component is related to IR independently.[13] More surprisingly, β-cell dysfunction was also found to be correlated with MetS components including body mass index (BMI), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG).[13-15] They also suggested that these relationships might be explained by the strong association of MetS components with high free fatty acid levels, which might be harmful to β-cell.[13]

Based on the aforementioned discussion, the role of the 1st ISEC is important and that the association between MetS and 1st ISEC is well documented. In this study, we tried to build clinical-metabolic models to detect the 1st ISEC deficiency (ISEC-D) early by using routine clinical parameters and MetS components in subjects without diabetes. If these high-risk subjects with abnormal glucose tolerance are identified, then early prevention and intervention could be initiated.

## METHODS

*Subjects*

In total, 89 subjects were enrolled in this study, including 49 with normal glucose tolerance (NGT) and 40 with pre-diabetes (PreDM). They were either self-referred or referred by health professionals, seeking a screening for diabetes. They had no history of diabetes in the past and, therefore, no medications for diabetes were taken at the time of the study. They were defined to be NGT or PreDM according to the criteria published by the American Diabetes Association in 2012.[16] Other than this, none of the subjects had a significant medical or surgical history. Before the study, they were instructed by physicians and dietitians not to receive any medication known to affect glucose or lipid metabolism and to stay on a staple diet for at least 1 week before the study. On the first day of the study, a complete routine workup was done to exclude the presence of cardiovascular, endocrine, renal, hepatic, and respiratory disorders. The study protocol had been approved by the hospital's institutional review board and ethics committee (CTH-101-2-5-028), and all subjects provided written informed consent prior to participation.

*Study protocol*

All tests were performed in the Clinical Research Center. On the day of the frequently sampled intravenous glucose tolerance test (FSIGT), after a 12-hour overnight fast, 1 catheter was placed on each arm. A bolus of 10% glucose water (0.3 g/kg) was given. Another bolus of regular human insulin (Novo Nordisk Pharmaceutical, Princeton, NJ) 0.05 units/kg was injected 20 minutes after glucose load. This insulin bolus was given because in subjects with severe insulin resistance, the effect of insulin on lower glucose was not seen during the test because the insulin level would be very low after the glucose loading. In the minimal model, the higher insulin level is essential for calculating insulin sensitivity. In the modified FSIGT, an insulin injection at the time point 20 minutes is the solution for this technical problem.[17] Blood samples for plasma glucose and insulin levels were collected at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, 180 minutes. The data were put into Bergman Minimal Model,[18] and then the insulin sensitivity, glucose effectivenes, and acute insulin response after the glucose load (AIRg) were obtained. The AIRg was considered as the 1st ISEC, and the product of insulin sensitivity and AIRg was the disposition index (DI).

The calculations of homeostasis model assessment of insulin resistance cell (HOMA-IR) function and homeostasis model assessment of β−cell (HOMA-β) function were also performed according to Matthew's equation.[19]

Plasma was separated within 1 hour of blood withdrawal and stored at -30° until the time of analysis. Plasma glucose was measured using a glucose analyzer with the glucose oxidase method (YSI Model 203, Scientific Division, Yellow Spring Instrument Company, Inc., Yellow Spring, OH). Plasma insulin was assayed by a commercial solid phase radioimmunoassay technique (Coat-A-Count insulin kit, Diagnostic Products Corporation, Los Angeles, CA) with intra- and inter-assay coefficients of variance of 3.3% and 2.5%, respectively. Serum TG was measured using the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film Corporation, Minato-Ku, Tokyo, Japan) with

the dry multilayer analytical slide method. Serum HDL-C concentration was determined with the enzymatic cholesterol assay method after dextran sulfate precipitation.

*Statistical analysis*

Data were shown as mean (standard deviation). An independent t test was used to evaluate the demographic data, clinical characteristics, and parameters derived from the tests between NGT and PreDM groups.

Subjects who had the lowest tertile of the 1st ISEC were defined as the ISEC-D group (insulin secretion deficiency group, tertile 1). The other two third of the subjects were classified as the ISEC-N group (insulin secretion normal group, tertiles 2 and 3).

The predictive performances of the variables for the ISEC-D such as MetS component and fasting plasma insulin (FPI) were evaluated individually first by logistic regression. Then, the receiver operating characteristic (ROC) curve of each variable (or model) was plotted as the sensitivity (true-positive rate, y axis) against the 1-specificity (false-positive rate on the X-axis). The area under the ROC curve (aROCcurve) was calculated by the trapezoidal rule, which was used to determine the predictive accuracy of the models. In general, a larger area corresponds to a better predictive accuracy of the variable (model).[20] These variables with a significantly higher ROCcurve were selected and used to build models to increase the accuracy of prediction.

Next, by using binary logistic regression, 3 models were build with the aforementioned variables. Whether to have insulin deficiency was defined as the dependent variable (0 for ISEC-D and 1 for ISEC-N), and the selected variables, i.e., BMI, HDL-C, FPG, and FPI were taken as the independent variables. We used BMI instead of the waist circumference because BMI highly correlates with the waist circumference (r=0.900 in men and r=0.889 in women).[21] Moreover, Chiu et al demonstrated that BMI is a better marker than "waist-hip ratio" to predict the first insulin secretion.[22] These independent variables were put into the models in a sequence from the least to the most significant aROC curves. They are shown as following:

Model 0: FPG

Model 1: FPG + BMI + HDL-C (MetS model)

Model 2: Model 1 + FPI (complete model)

The Hosmer-Lemeshow test was used to assess how well these models fit the data. The Omnibus test was used to test the models to significantly explain the variation of the dependent variable. A comparison of the aROC curves of the models was performed using the method developed by Hanley and McNeil.[20] From these ROC curves, the optimal cut-point values with the highest sensitivity and specificity were selected. In short, if the value derived from the equation is higher than the specified cutoff point, the chance of having ISEC-D is high. Finally, from binary logistic regression, the equation was further build for each model.

To verify the accuracies of our equations, we compared our models with HOMA-β, the widely used surrogate for β-cell function. To do this, the ROC curve of HOMA-β was plotted and an ROC was calculated after log transformation. All statistical analyses were performed using the SPSS, version 13.0 (SPSS Inc., Chicago, IL USA). The *P* values less than .05 were considered statistically significant. On the contrary, the *P* value more than .05 for the Hosmer-Lemeshow test was regarded as the goodness of fit for logistic regression models.

## RESULTS

The demographic data and other parameters of NGT and PreDM are shown in **Table 1**. After grouping, comparisons betweenISEC-D and ISEC-N with the t test were repeated again (**Table 2**). Subjects in the ISEC-D group had lower BMI, HOMA-IR, HOMA-β, and FPI and higher FPG those in the ISEC-N group. No statistically significant differences were observed in age, gender, systolic blood pressure (SBP), diastolic blood pressure, and TG levels. The mean plasma glucose and insulin levels at each time point during the FSIGT of the ISEC-D and ISEC-N groups are shown in **Figure 1**. During the FSIGT, subjects with ISEC-D had lower insulin concentrations than those with ISEC-N at each time point before 20 minutes.

The results of the aROC curves, Hosmer-Lemeshow goodness-of-fit, and Omnibus test of the studied parameters and models are shown in **Table 3**. All independent variables and models except SBP fit the data, which was determined by the Hosmer-Lemeshow test. Moreover, age, BMI, FPG, HDL-C, Log FPI, Log HOMA-β, Model 1, and Model 2 significantly explained the variation for the dependent variable. Among the clinical-metabolic variables, FPG, BMI, HDL-C, and log FPI had greater aROC curves than that of the diagonal reference line. They were selected to be put into the models as mentioned in the method section. The results of comparison between the aROC of the models against either simple clinical parameters or HOMA-β are shown in **Table 4**. It can be noted that after adding BMI and HDL-C into Model 0, Model 1 showed improvement in the aROC. However, when log FPI was put into Model 1, Model 2 did not show further improvement (**Tables 3 and 4**). Even so, the aROC

of Model 2 was still higher than that of HOMA-β. The equations build from Models 1 and 2 are shown as follows: $P=1/(1-e^{-x})$, where x=0.198-0.267*(BMI)+0.694*(FPG)+1.600* (HDL-C) for Model 1, and x =-0.357–0.218*(BMI)+0.747*(FPG)+1.687*(HDL-C)–0.758*(logFPI) for Model 2, respectively. In these equations, P refers to the probability of having ISEC-D. The 2 final models are shown in **Table 5**.

**Figure 2** demonstrates the ROC curves of these models. The arbitrarily selected risk score cutoff of Model 0 is 0.303, which corresponds to the FPG 5.551 mmol/L and has a sensitivity of 69.0% and a specificity of 66.3%. For Model 1, the cutoff value is 0.356; the sensitivity increases to 84.0% and specificity to 74.0 %. Interestingly, after adding the logFPI into Model 1, although the aROC is higher (selected risk score cutoff 0.35), Model 2 does not have a better sensitivity and specificity than Model 1 specificity of Model 1 and Model 2 is 76.0% and 75.0%, respectively. At the same time, aROC of HOMA-β is less than that of Model 1 (0.73, and 0.804, respectively). The cutoff point of 0.250 yields a 72.4% of sensitivity and a 63.3% of specificity.

## DISCUSSION

In this study, we tried to build clinical-metabolic models using minimal clinical variables, MetS components, and FPI to predict ISEC-D in subjects without diabetes. Our data have shown that by using only the FPG, BMI, and HDL-C (Model 1), ISEC-D could be estimated with a satisfactory sensitivity of 84.0% and

**Table 1.** The baseline clinical characteristics in the groups of normal glucose tolerance and pre-diabetes.

| | Normal glucose tolerance | Pre-diabetes | *P* value |
|---|---|---|---|
| n | 49 | 40 | |
| Gender (M/F) | 22/27 | 20/20 | .63 |
| Age (y) | 42.7 (17.1) | 54.4 (11.9) | <.001 |
| Body mass index (kg/m$^2$) | 26.1 (5.8) | 24.7 (3.1) | .15 |
| Systolic blood pressure (mm Hg) | 117.6 (10.9) | 121.0 (14.7) | .24 |
| Diastolic blood pressure (mm Hg) | 73.9 (6.8) | 76.1 (8.5) | .23 |
| Fasting plasma glucose (mmol/L) | 4.7 (0.4) | 6.4 (0.4) | <.001 |
| HDL-cholesterol (mmol/L) | 1.1 (0.4) | 1.1 (0.3) | .67 |
| Triglyceride (mmol/L) | 1.2 (0.6) | 1.4 (0.6) | .32 |
| Log (fasting plasma insulin (mU/L)) | 1.5 (0.6) | 1.4 (0.6) | .25 |
| Log HOMA-IR | 2.2 (0.7) | 2.1 (0.6) | .88 |
| Log HOMA-β | 0.8 (0.7) | 0.5 (0.6) | .04 |
| Log (first-phase insulin secretion [μU/min]) | 2.9 (0.8) | 2.0 (0.7) | <.001 |
| Log(Insulin sensitivity) ($10^{-4}$/[min·pmol·L) | -0.03 (0.67) | 0.04 (0.85) | .43 |
| Glucose effectiveness ($10^{-2}$·dL·[min·kg]) | 0.020 (0.010) | 0.014 (0.008) | <.01 |

The data is shown as mean (standard deviation).1st ISEC, first-phase insulin secretion (acute insulin response after glucose load); HDL-C, high-density lipoprotein cholesterol; FPI: fasting plasma insulin; HOMA-IR and HOMA-β, homeostasis model assessment of insulin resistance and β-cell function.

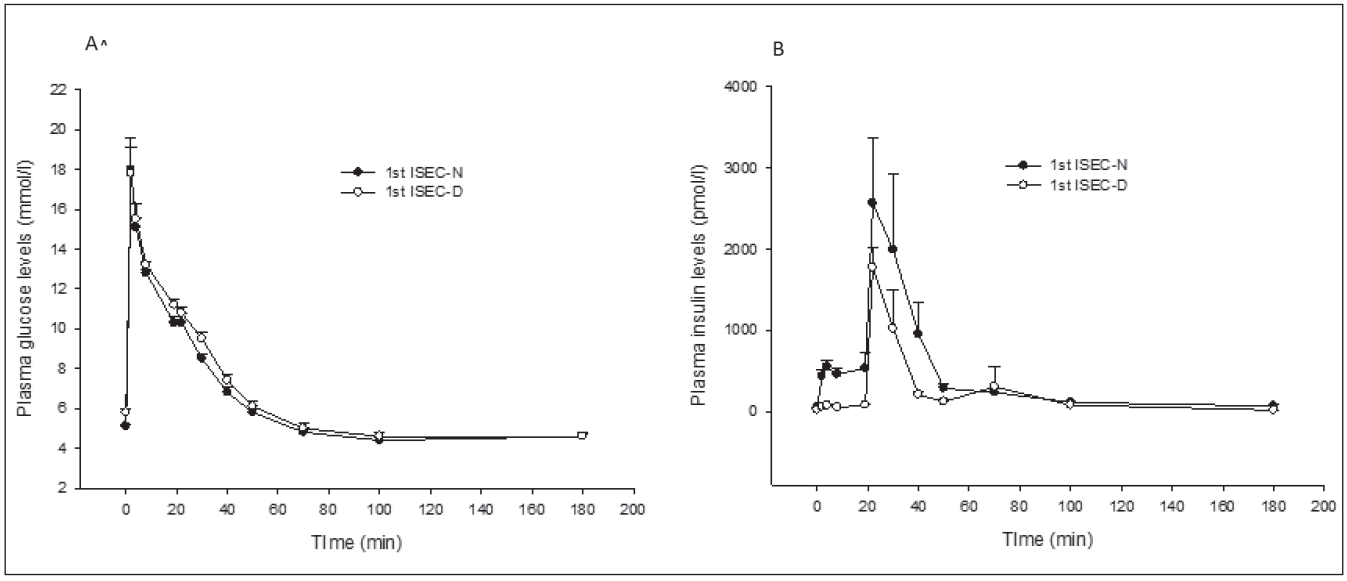


**Figure 1.** Plasma glucose (Panel A) and insulin concentration (Panel B) in each time point during frequently sampled intravenous glucose tolerance test of the ISEC-N and ISEC-D groups.

**Table 2.** The baseline clinical characteristics in the subjects with normal and deficient first insulin secretion.

| | ISEC-N | ISEC-D | *P* value |
|---|---|---|---|
| n | 60 | 29 | |
| (NGT/pre-diabetes) | 40/20 | 9/20 | <.01 |
| Gender (male/female) | 30/30 | 12/17 | .45 |
| Age (y) | 46.3 (17.8) | 50.8 (11.7) | .17 |
| Body mass index (kg/m$^2$) | 26.6 (5.0) | 23.2 (3.6) | <.01 |
| Systolic blood pressure (mm Hg) | 119.6 (12.2) | 118.5 (15.1) | .72 |
| Diastolic blood pressure (mm Hg) | 75.1 (7.7) | 74.5 (7.8) | .77 |
| Fasting plasma glucose (mmol/L) | 5.2 (1.0) | 5.9 (0.8) | <.001 |
| HDL-cholesterol (mmol/L) | 1.1 (0.3) | 1.2 (0.3) | .05 |
| Triglyceride (mmol/L) | 1.3 (0.6) | 1.3 (0.6) | .91 |
| Log (fasting plasma insulin) (μU/L) | 1.6 (0.5) | 1.1 (0.7) | <.01 |
| Log (HOMA-IR) | 2.3 (0.6) | 1.9 (0.7) | .01 |
| Log (HOMA–β) | 0.9 (0.6) | 0.3 (0.7) | <.001 |
| Log (first-phase insulin secretion) (μU/min) | 2.9 (0.6) | 1.5 (0.5) | <.001 |
| Log (insulin sensitivity) ($10^{-4}$·min$^{-1}$·pmol$^{-1}$·L$^{-1}$) | -0.2 (1.0) | 0.2 (0.6) | .03 |
| Glucose effectiveness ($10^{-2}$·dL·min$^{-1}$·kg$^{-1}$) | 0.019 (0.010) | 0.015 (0.08) | .06 |

ISEC-D, Deficient first-phase insulin secretion; ISEC-N, normal first-phase insulin secretion; NGT, normal glucose tolerance; HDL-C, high-density lipoprotein cholesterol; FPI: fasting plasma insulin; HOMA-IR and HOMA-β, homeostasis model assessment of insulin resistance and β-cell function.

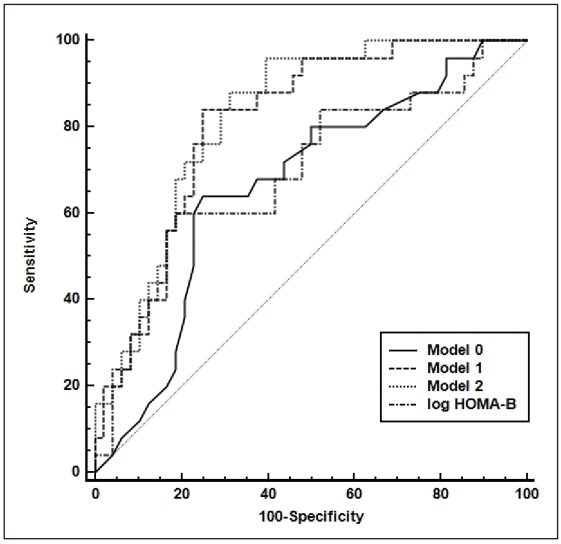


**Figure 2.** Area under the receiver-operating characteristic (ROC) curve of the models in the study groups.

specificity of 74.0%. At the same time, although FPI is considered to be closely related to the 1st ISEC, it is not a routinely available item done in medical settings. Therefore, we did not put FPI into Model 1. However, the result of adding FPI into Model 2 was disappointing. The aROC did not increase as we had expected. Even so, the performance of Model 1 is better than that of HOMA-β. However, we believe that the results of our study are not only interesting but also practical. By using these models, subjects with ISEC-D could be identified, and early intervention could be applied to delay the occurrence of diabetes.

Among the MetS components, only FPG, BMI, and HDL-C were selected to be put into the models in our study. From the physiological point of view, the main purpose of insulin secretion is to maintain the plasma glucose levels in the normal range. To be more specific, the 1st ISEC is the rapid response to the increase of the ambient glucose level. It was shown that this stage of insulin secretion is surprisingly vulnerable and disappears early in subjects with PreDM.[7,23] Even in subjects with NGT, a decrease in the 1st ISEC could also be found.[24,25] Thus, it is not surprising that FPG had the greatest power to predict ISEC-D among the individual MetS components (aROC=70.9%).

BMI was the second strong component contributing to the 1st ISEC in our study (aROC=68.8%). This relationship could be easily explained by that obesity has been proved to be positively associated with greater β-cell mass and better insulin secretion[13,26,27] in both diabetic and non-diabetic subjects. Interestingly, after adding BMI into FPG for analysis, the aROC increased from 66.5% to 76.8% but no significant difference was observed (*P*=.089, data was not shown). This unexpected finding might be attributed to the following 2 reasons: First, the 1st ISEC was associated with FPG and BMI separately in simple correlation. At the same time, it is also well-known that the FPG was tightly correlated with BMI. In other words, part of the positive relationship between 1st ISEC and BMI was acting through FPG. This relationship "diluted" the interaction between 1st ISEC and BMI and made this relationship insignificant. Second, it should be noted that the average BMI was approximately 25.4 (3.0) kg/m$^2$ in our study, which was still in the range of overweight for Asians. Most of other studies done in the Western world had a much higher BMI.[8,23] This lower BMI might have a weaker impact on insulin secretion. By enrolling subjects with a wider range of BMI in future studies, the difference might become statistically significant.

Other than FPG and BMI, HDL-C was the third

and last component selected to be put into the model that had an aROC of 63.6%. Consistent with the results of earlier studies, we also found an inverse relationship between 1st ISEC and HDL-C.[13] This relationship could be explained by the finding that HDL-C is positively related to insulin sensitivity and, in the early stage of diabetes, the insulin secretion is negatively correlated with insulin sensitivity.[13,14] In other words, insulin sensitivity is the intermediary between HDL-C and 1st ISEC. As mentioned earlier, no significant increase was observed in the aROC after adding BMI into Model 1. However, after putting both BMI and HDL-C into Model 1, the aROC significantly increased from 70.9% to 80.4% (*P*=.034). This implies that both obesity and HDL-C may affect the 1st ISEC but not through the same mechanisms. Interestingly, different from HDL-C, TG was not selected into our models. Hanley et al. demonstrated that HDL-C correlated with FPS in non-diabetic subjects but TG did not, which was in accordance with our results.[13] Moreover, Gower et al suggested that the association of β-cell function with TG level differed with ethnicity, which further confirmed our finding.[14]

FPI, which is not a routine item of the biochemistry panel, is well established to be associated with insulin secretion.[10,13,19,28] In line with the findings of Hanley's study,[13] our study also demonstrated that FPI had a similar aROC as FPG to predict ISEC-D (72.6% vs. 70.9%, respectively, *P*=.845). After putting FPI into Model 1, the aROC increased from 80.4% to 82.3%

**Table 3.** Area under the receiver-operating characteristic curves (ROC curves) of clinic-metabolic variables and models predicting first phase of insulin secretion deficiency.

| Models | Area under the ROC curve±SE (95% CI) | *P* value (Hosmer-Lemeshow) | *P* value (Omnibus test) |
|---|---|---|---|
| Age | 0.512±0.0670 (0.375-0.649) | .24 | .05 |
| Gender | 0.521±0.070 (0.383-0.658) | | .73 |
| BMI | 0.688±0.060 (0.570-0.807) | .27 | .01 |
| Systolic blood pressure | 0.476±0.069 (0.342-0.611) | .03 | .97 |
| Diastolic blood pressure | 0.488±0.073 (0.345-0.631) | .09 | .77 |
| Fasting plasma glucose (Model 0) | 0.709±0.068 (0.591-0.827) | .11 | <.01 |
| Triglyceride | 0.451±0.069 (0.315-0.587) | .76 | .83 |
| HDL-Cholesterol | 0.636±0.070 (0.507-0.781) | .06 | .05 |
| Log (FPI) | 0.726±0.062 (0.605-0.848) | .59 | <.01 |
| Log HOMA-β | 0.730±0.058 (0.616-0.845) | .24 | .01 |
| Model 1 (FPG, HDL-C, BMI) | 0.804±0.051 (0.705-0.903) | .26 | <.01 |
| Model 2 (FPG, HDL-C, BMI, FPI) | 0.823±0.048 (0.729-0.917) | .96 | <.01 |

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; FPI, fasting plasma insulin; HOMA-IR and HOMA-β, homeostasis model assessment of insulin resistance and β–cell function.

**Table 4.** The comparison of area under the receiver-operating characteristic curves (aROC curves) of clinic-metabolic variables and models predicting the first-phase of insulin secretion deficiency.

| Pairwise comparison test between aROC curves of each models | *P* value |
|---|---|
| Model 0 vs. BMI | .43 |
| Model 0 vs. HDL-C | .80 |
| Model 0 vs. log FPI | .92 |
| Model 1 vs. Model 0 | .03 |
| Model 1 vs. log HOMA-β | .05 |
| Model 2 vs. Model 0 | .02 |
| Model 2 vs. Model 1 | .48 |
| Model 2 vs. log HOMA-β | .01 |

BMI, Body mass index; HDL-C, high-density lipoprotein cholesterol; FPI, fasting plasma insulin; HOMA-IR and HOMA-β, homeostasis model assessment of β-cell function; Model 0: fasting plasma glucose; Model 1: fasting plasma glucose + BMI + HDL-C; Model 2, Model 1+ log(FPI).

**Table 5.** Each variable with odds ratio estimate and standard error in the 2 models predicting first insulin secretion deficiency.

| MetS | Coefficient of independent variable | Standard error | Odds ratio estimate |
|---|---|---|---|
| FPG | 0.694 | 0.313 | 2.00 |
| BMI | -0.267 | 0.098 | 0.77 |
| HDL-C | 1.600 | 0.889 | 4.95 |
| Constant | 0.198 | 2.838 | 1.22 |
| **MetS + FPI** | | | |
| FPG | 0.747 | 0.329 | 2.11 |
| BMI | -0.218 | 0.106 | 0.80 |
| HDL-C | 1.687 | 0.906 | 5.40 |
| FPI | -0.758 | 0.529 | 0.47 |
| Constant | -0.357 | 2.967 | 0.70 |

MetS, Metabolic syndrome; FPG, fasting plasma glucose; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; FPI, fasting plasma insulin.

but this increment did not reach statistical significance (*P*=.482). Similar to the relationship between BMI and 1st ISEC, we postulated that the effect of FPI on the 1st ISEC was "diluted" by the tight correlation between BMI and FPI (r=0.431, *P*=.000). This indicates that BMI plays a vital role between insulin sensitivity and insulin secretion.

It would be interesting to compare our models with the most widely used surrogate for β-cell function, the HOMA-β. Model 0 showed a non-inferior prediction for ISEC-D subjects (aROC 0.709 for Model 0 vs. 0.730 for HOMA-β). After adding HDL-C and BMI, Model 1 bore a borderline higher aROC compared with HOMA-β (0.804 vs. 0.730, respectively, *P*=.052). Finally, a significant improvement of the aROC was reached after adding FPI into Model 2 (0.823 for model 2 vs 0.730 for HOMA-β, respectively *P*=.013). Our findings show that simply by using the MetS components, the prediction accuracy is better than HOMA-β. However, it should be mentioned that although both our models and HOMA-βare measurement for β-cell function, they are conceptually different. From the equation, it is obvious that HOMA-β reflects the insulin secretion in a "static condition." At the same time, the 1st ISEC is the dynamic secretion of the β-cell after the glucose loading. Since not quantifying from the same angle, the correlation between these 2 methods should not be tight in the first place. Moreover, as mentioned earlier, both BMI and HDL-C are important factors to affect the 1st ISEC independently. They are not considered in the HOMA-β equation. Thus, it is not surprising that Model 2 has a much higher and significant aROC than that of the HOMA-β.

To the best of our knowledge, the current study is the first and only one trying to develop clinical-metabolic models to predict ISEC-D in subjects without diabetes. The prediction accuracy of our prediction models is satisfactory. However, there are still some limitations in our study. First, family history was not evaluated in our study. It has been established that non-diabetic subjects with a family history of T2DM have impaired β cell function and reduced β cell response to IR than those without.[25] The predictive accuracy should be higher if we put family history into the models. Second, as mentioned earlier, the population size in our study was relatively, small and a larger sample population will make our results convincing. Moreover, if we had a larger cohort, a certain percentage could be separated as a validation group to further verify our results. Thus, the equations derived from the models could be tested in this group. Hopefully, in the future, we could confirm our equations and models in a different cohort. Finally, the oral glucose tolerance test was not done in the study. Post-challenge 120-minute glucose and insulin levels—which represent a "dynamic" aspect of the β-cell function than FPG and FPI levels—were not measured. Adding these 2 factors should further increase the predictive power for the 1st ISEC. However, even with these limitations, we still believe that our equations could be easily and accurately used in clinical settings.

In conclusion, by only using MetS components (FPG, BMI, and HDL-C), ISEC-D could be predicted with an acceptable sensitivity of 84.0% and a specificity of 74.0%, which is better than HOMA-β. However, after adding FPI into Model 2, the predictive power of Model 2 did not increase. We believe that the equation-derived MetS components could be widely used in clinical settings and early detection of non-diabetic subjects with a high risk for T2DM in the future.

**Acknowledgments**

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## REFERENCES

**1.** DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. A balanced overview. Diabetes Care 1992;15:318-68.
**2.** Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. Diabet Med 1998;15:297-303.
**3.** Fukushima M, Usami M, Ikeda M, Nakai Y, Taniguchi A, Matsuura T, Suzuki H, Kurose T, Yamada Y, Seino Y. Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. Metabolism 2004;53:831-5.
**4.** Lin JD, Chen YL, Hsu CH, Wu CZ, Hsieh AT, Hsieh CH, Chang JB, Liang YJ, Pei D. Beta-cell function and insulin sensitivity at various degrees of glucose tolerance in Chinese subjects. Diabetes Res Clin Pract 2013;100:391-7.
**5.** Cerasi E, Luft R. Plasma-Insulin Response to Sustained Hyperglycemia Induced by Glucose Infusion in Human Subjects. Lancet 1963;2:1359-61.
**6.** Caumo A, Luzi L. First-phase insulin secretion: does it exist in real life? Considerations on shape and function. Am J Physiol Endocrinol Metab 2004;287:E371-85.
**7.** Pratley RE, Weyer C. The role of impaired early insulin secretion in the pathogenesis of Type II diabetes mellitus. Diabetologia 2001;44:929-45.
**8.** van Haeften TW, Pimenta W, Mitrakou A, Korytkowski M, Jenssen T, Yki-Jarvinen H, Gerich JE. Disturbances in beta-cell function in impaired fasting glycemia. Diabetes 2002;51 Suppl 1:S265-70.
**9.** Del Prato S, Tiengo A. The importance of first-phase insulin secretion: implications for the therapy of type 2 diabetes mellitus. Diabetes Metab Res Rev 2001;17:164-74.
**10.** Weiss R, Caprio S, Trombetta M, Taksali SE, Tamborlane WV, Bonadonna R. Beta-cell function across the spectrum of glucose tolerance in obese youth. Diabetes 2005;54:1735-43.
**11.** Vega GL. Results of Expert Meetings: Obesity and Cardiovascular Disease. Obesity, the metabolic syndrome, and cardiovascular disease. Am Heart J 2001;142:1108-16.
**12.** Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683-9.
**13.** Hanley AJ, Wagenknecht LE, D'Agostino RB, Jr., Zinman B, Haffner SM. Identification of subjects with insulin resistance and beta-cell dysfunction using alternative definitions of the metabolic syndrome. Diabetes 2003;52:2740-7.
**14.** Gower BA, Ard JD, Hunter GR, Fernandez J, Ovalle F. Elements of the metabolic syndrome: association with insulin sensitivity and effects of ethnicity. Metab Syndr Relat Disord 2007;5:77-86.
**15.** Hsieh CH, Wu CZ, Hsiao FC, Lin JD, Li JC, Wan HL, Kuo SW, Hung YJ, Su CC, Pei D. The impact of metabolic syndrome on insulin sensitivity, glucose sensitivity, and acute insulin response after glucose load in early-onset type 2 diabetes mellitus: Taiwan Early-Onset Type 2 Diabetes Cohort Study. Metabolism 2008;57:1615-21.
**16.** American Diabetes Association. Diagnosis and Classfication of Diabetes Mellitus. Diabetes Care 2012;35 Suppl 1:S1-2.
**17.** Welch S, Gebhart SS, Bergman RN, Phillips LS. Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. J Clin Endocrinol Metab 1990;71:1508-18.
**18.** Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol 1979;236:E667-77.
**19.** Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
**20.** Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-43.
**21.** Ko GT, Chan JC, Cockram CS, Woo J. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. Int J Obes Relat Metab Disord 1999;23:1136-42.
**22.** Chiu KC, Chuang LM, Yoon C. Comparison of measured and estimated indices of insulin sensitivity and beta cell function: impact of ethnicity on insulin sensitivity and beta cell function in glucose-tolerant and normotensive subjects. J Clin Endocrinol Metab 2001;86:1620-5.
**23.** Mari A, Tura A, Pacini G, Kautzky-Willer A, Ferrannini E. Relationships between insulin secretion after intravenous and oral glucose administration in subjects with glucose tolerance ranging from normal to overt diabetes. Diabet Med 2008;25:671-7.
**24.** Godsland IF, Jeffs JA, Johnston DG. Loss of beta cell function as fasting glucose increases in the non-diabetic range. Diabetologia 2004;47:1157-66.
**25.** Bonadonna RC, Stumvoll M, Fritsche A, Muggeo M, Haring H, Bonora E, van Haeften TW. Altered homeostatic adaptation of first- and second-phase beta-cell secretion in the offspring of patients with type 2 diabetes: studies with a minimal model to assess beta-cell function. Diabetes 2003;52:470-80.
**26.** Kloppel G, Lohr M, Habich K, Oberholzer M, Heitz PU. Islet pathology and the pathogenesis of type 1 and type 2 diabetes mellitus revisited. Surv Synth Pathol Res 1985;4:110-25.
**27.** Pei D, Hsiao CF, Hung YJ, Hsieh CH, Fang SC, Lian WC, Hsu WL, Fu CC, Chen HD, Kuo SW. The insulin sensitivity, glucose sensitivity, and acute insulin response to glucose load in adolescent type 2 diabetes in Taiwanese. Diabetes Metab Res Rev 2006;22:26-33.
**28.** Reaven GM. Insulin secretory function in type 2 diabetes: Does it matter how you measure it? J Diabetes 2009;1:142-50.