original article

Predicting glucose intolerance with normal fasting plasma glucose by the components of the metabolic syndrome

Dee Pei,* Jiunn-Diann Lin,† Du-An Wu,‡ Chang-Hsun Hsieh,§ Yi-Jen Hung,§ Shi-Wen Kuo,† Ko-Lin Kuo,|| Chung-Ze Wu,§ Jer-Chuan Li‡

From the *Department of Internal Medicine, Cardinal Tien Hospital, College of MEdicine, Fu Jen Catholic University, Xindian, Taiwan, ROC, †Division of Endocrinology and Metabolism, Department of Internal Medicine, Buddhist Tzu Chi General Hospital, Taipei Branch, College of Medicine, Tzu Chi University, Taiwan, ROC, ‡Division of Endocrinology and Metabolism, Department of Internal Medicine, Buddhist Tzu Chi General Hospital, College of Medicine, Tzu Chi University, Hualien, Taiwan, ROC, §Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan, ROC and the ||Division of Nephrology, Buddhist Tzu Chi General Hospital, Taipei Branch, Taiwan, ROC.

Correspondence and reprint requests: Jer-Chuan Li MD · Division of Endocrinology and Metabolism · Buddhist Tzu Chi General Hospital · No 707 · Sec 3 · Jhongyang Road · Hualien 97002 · Taiwan · ROC · T: +886 38 561825 · F: +886 38 577161 lijc.lijc@msa.hinet.net · Accepted for publication April 2007

Ann Saudi Med 2007; 27(5): 339-346

BACKGROUND: Surprisingly, it is estimated that about half of type 2 diabetics remain undetected. The possible causes may be partly attributable to people with normal fasting plasma glucose (FPG) but abnormal postprandial hyperglycemia. We attempted to develop an effective predictive model by using the metabolic syndrome (MeS) components as parameters to identify such persons.

SUBJECTS AND METHODS: All participants received a standard 75-g oral glucose tolerance test, which showed that 106 had normal glucose tolerance, 61 had impaired glucose tolerance, and 6 had diabetes-on-isolated postchallenge hyperglycemia. We tested five models, which included various MeS components. Model 0: FPG; Model 1 (clinical history model): family history (FH), FPG, age and sex; Model 2 (MeS model): Model 1 plus triglycerides, high-density lipoprotein cholesterol, body mass index, systolic blood pressure and diastolic blood pressure; Model 3: Model 2 plus fasting plasma insulin (FPI); Model 4: Model 3 plus homeostasis model assessment of insulin resistance. A receiver-operating characteristic (ROC) curve was used to determine the predictive discrimination of these models.

RESULTS: The area under the ROC curve of the Model 0 was significantly larger than the area under the diagonal reference line. All the other 4 models had a larger area under the ROC curve than Model 0. Considering the simplicity and lower cost of Model 2, it would be the best model to use. Nevertheless, Model 3 had the largest area under the ROC curve.

CONCLUSION: We demonstrated that Model 2 and 3 have a significantly better predictive discrimination to identify persons with normal FPG at high risk for glucose intolerance.

Type 2 diabetes mellitus (T2DM) is a serious chronic disease with disordered carbohydrate metabolism that places a heavy burden on health services and patients due to its morbidity and mortality. The prevalence T2DM is continuously growing worldwide.[1,2] Remarkably, glucose intolerance (eg., impaired glucose intolerance [IGT] and diabetes) is frequently asymptomatic and the delay from disease onset to clinical diagnosis may exceed at least 4 to 7 years.[3] Strikingly, tissue damage progresses before diagnosis.[4-7] Therefore, early diagnosis and intervention are important in reducing the burden of diabetic complications. In one study, it was estimated that up to 50% of persons with diabetes were undetected or newly diagnosed.[8-10] One of the possible causes may be attributable to a normal fasting plasma glucose (FPG) but abnormal postprandial hyperglycemia, i.e., IGT or diabetes-on-isolated postchallenge hyperglycemia (DM-on-IPH) may also be responsible.[11]

The prevalence of IGT in Taiwan established in 1996 was 15.5%, which was higher than the prevalence of diabetes (9.2%).[12] However, in Taiwan, about 40% of diabetics have not yet been diagnosed.[13] Moreover, the mortality of T2DM is growing and was the fourth

leading cause of death in Taiwan in 2002[14] with about a 6.3-fold increase over a period of 30 years.[15] Thus, we are encouraged to establish a simple and efficient predictive model to reduce the incidence of T2DM by early prediction and intervention.

The diagnostic criteria of diabetes was revised by the American Diabetes Association (ADA)[16] in 1997. The main modifications emphasized using only FPG to diagnose diabetes and lower the cutoff point to 7.0 mmol/L. Furthermore, a new category of "impaired fasting glucose" (IFG) was introduced. Subsequently, the World Health Organization (WHO) criterion for the diagnosis of diabetes[17] was also published. It retained the lower cutoff for FPG and, at the same time, suggested that the oral glucose tolerance test (OGTT) was still a useful method for diagnosing diabetes. However, after both criteria have been reported, many studies have found that the concordance between them was not so good.[18-23] Furthermore, according to ADA criteria, whether persons with normal FPG are truly non-diabetic is an emerging problem. It could be noted that people with either DM-on-IPH[11] or diabetes-on-isolated fasting hyperglycemia are difficult to detect by the 1997 ADA criteria. To solve these problems, many authors have suggested different methods to increase the sensitivity to detect diabetes, such as the level of glycated hemoglobin[24] or a predictive risk score model.[25]

Metabolic syndrome (MeS) is a cluster of metabolic factors, including central obesity, hypertension, dyslipidemia, and glucose intolerance. People with MeS are found to have a high risk for cardiovascular disease and T2DM. The central pathophysiology of MeS is generally agreed to be insulin resistance,[26-28] which is also central to T2DM.[29] The term "MeS" was coined by WHO in 1998 as an attempt at eraly detection of subjects at high risk for diabetes and cardiovascular diseases.[16] Three years later, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) had also provided another similar, but simple and clinically useful definition of MeS.[30]

In this study, we were interested in and focused on persons with normal FPG who had either normal glucose tolerance (NGT), IGT, or DM-on-IPH. We conducted a binary logistic regression analysis to obtain a model to estimate the probability of having dysglycemia (i.e., IGT and DM-on-IPH in our study). The components of MeS were put into the proposed models. A receiver-operating characteristic (ROC) curve[31] was used to determine the predictive discrimination power of these models with the hope of obtaining a simple and efficient predictive model that could be widely acceptable in clinical or health care settings to identify subjects at high risk for glucose intolerance.

SUBJECTS AND METHODS

A total of 513 participants were enrolled and received the standard 75-g OGTT in Tri-Service General Hospital from 1998 to 2001. Subjects were either self-referred or referred by health professionals, seeking a screening for diabetes. They had no history of diabetes in the past. After excluding frank diabetes and IFG, only 424 cases were suitable for further study. Among them, 82 were classified as IGT (defined as 2-h PG during OGTT between 7.8 and 11.1 mmol/L and FPG < 6.1 mmol/L), another 6 as DM-on-IPH (defined as FPG < 6.1 mmol/L and 2-h plasma glucose (2-h PG during OGTT ≥ 11.1 mmol/L).[23] However, due to incomplete data on family history or other parameters, only 106 subjects with NGT, 61 with IGT and 6 with DM-on-IPH were available for this study. None of the patients had significant medical or surgical history. Before the study, they were instructed by the doctors and dietitians not to receive any medication known to affect glucose or lipid metabolism and to stay on a stable diet for at least one week before the study. On the day of the visit, each subject had a complete routine work-up to rule out the presence of cardiovascular, respiratory, renal or endocrine disorders. The study had been approved by the hospital ethics committee, and the purpose and the potential risks of the study were explained to the subjects before obtaining their written consent to participate.

On the day of the test, a standard 75-g OGTT was carried out for 3 hours after a 12-h overnight fast. Blood samples were obtained for the determination of glucose and insulin concentrations at baseline (time 0 min) and 30-minute intervals for 3 hours. Other than the OGTT, homeostasis model assessment (HOMA) was also used to estimate the insulin sensitivity (HOMA-IR=fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5). HOMA is a mathematical model based on glucose and insulin interaction in different organs, including the pancreas, liver, and peripheral tissues.[32] The model determines insulin sensitivity or insulin resistance.[32,33] Application of HOMA has also been used in epidemiological studies.[32,34]

Plasma was separated from blood within 1 hour and stored at −30°C until analyzed. Plasma glucose was determined by the glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Spring Instrument Company, Inc., Yellow Spring, Ohio, USA). Insulin[35] was measured by a commercial radio-immunoassay kit (Coat-A-Count insulin kit, Diagnostic Products Corporation, Los Angeles, California, USA).

Both triglycerides (TG) and total cholesterol (TC)

Table 1. Anthropometric and metabolic characteristics of study subjects.

Demographic data	NGT	Dysglycemia
Number	106	67
Sex (M/F)	50/56	37/30
Age	35.4±1.2	41±1.6*
BMI (kg/m^2)	22.8±0.4	24.7±0.5*
SBP (mmHg)	115.1±1.3	124.9±2.3*
DBP (mmHg)	74.7±1.0	80.7±1.5
TC (mmol/ L)	3.6±0.9	4±0.1
TG (mmol/ L)	1.3±0.1	1.7±0.1*
HDL-C (mmol/L)	2.74±0.23	0.77±0.04
FPG (pmol/ L)	5.1±0.04	5.3±0.1
2-h PG	5.6±0.1	9.1±0.2*
FPI (pmol/ L)	48.4±2.6	85.5±14.7*
HOMA-IR	1.6±0.9	2.8±0.5*

NGT, normal glucose tolerance group; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; 2-h PG, 2-hour plasma glucose during after 75-g OGTT; HOMA-IR, homeostasis model assessment of insulin resistance. * versus NGT group, $P< 0.05$; Data are shown as mean±SE.

were measured using the dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film Corporation, Minato-Ku, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) concentration was determined by an enzymatic cholesterol assay method after dextran sulfate precipitation.

Since there were only 6 subjects with DM-on-IPH and the purpose of our study was to predict glucose intolerance only, we combined both the IGT group and DM-on-IPH group into one as a "dysglycemia group". Although there are a number of MeS definitions, the NCEP ATP III-defined MeS criteria has been widely applied in clinical and epidemiological research. Therefore, we employed these criteria in our study. However, since we did not have data on waist circumference, we used BMI instead.

Using binary logistic regression analysis we put all interesting factors into the model for model selection. Five models were proposed to identify normal and abnormal glucose metabolism. Each model included the different components of the MeS. The five models were as follows:

- Model 0: FPG
- Model 1 (clinical model): family history, FPG, age and sex
- Model 2 (the MeS model): all risk factors in Model 1 plus TG, HDL-C, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP)
- Model 3 (insulin was added for evaluating the effect of insulin level on the model): all risk factors in Model 2 plus fasting plasma insulin (FPI)
- Model 4 (HOMA-IR was added): all risk factors in Model 3 plus HOMA-IR.

For Model 0, the FPG was forced into the model. The 95% confidence intervals were also calculated for the binary logistic regression analysis. The Hosmer-Lemeshow test was used to assess the goodness of fit of these models. Calculations were performed using the SPSS (10.0) statistical package (SPSS Inc., Chicago, IL, USA). A *P*-value (two-sided) < 0.05 was considered to be significant. For each individual in every model, an estimated probability of an abnormal event (occurrence of dysglycemia) was also calculated. We then used the estimated probability to predict whether a subject was at high risk for dysglycemia (see the appendix). A plot of the ROC curve, which is a line diagram with the sensitivity plotted vertically with the false positive rate on the horizontal axis, and is determined by the trapezoidal rule, was used to choose the cutoff of values. The diagonal line represents results no better than chance. The ROC curve is a mathematical method used to assess the predictive discrimination of a test.[31] The statistical significance of differences in areas under ROC curves between any two models were estimated by likelihood ratio testing.

RESULTS

Table 1 shows the demographic data of the study subjects. From the selection criteria, it is not surprising that all subjects had normal FPG. The dysglycemic group was older and had a higher BMI, SBP, TG, 2-h PG, FPI and HOMA-IR than the NGT group. All data were adjusted for age and BMI.

Model 0 had only one risk factor (FPG) and was regarded as the "baseline model". The area under the ROC curve was significantly greater than the area under the curve of the diagonal reference line (Panel A, Figure 1), which means that the prediction rate could be improved significantly even with use of FPG alone.

Table 2 presents the areas under the ROC curves, their Hosmer-Lemeshow goodness-of-fit statistics, and tests of the statistical significance of the differences between various models by the likelihood ratio test. When compared to Model 0, all of the other 4 models have a larger area under the ROC curve (better prediction rate). Moreover, by putting more variables into the

Table 2. Area under the receiver-operating characteristic (ROC) curve and their comparisons for models predicting dysglycemia.

Models* and model comparisons	Area under the ROC curve (95% CI),%	*P* value (Hosmer-Lemeshow)**	*P* values for model comparisons (likelihood ratio tests)***
Models			
0	64.8 (56.1-73.6)	0.001	
1	67.3 (59-75.6)	0.303	
2	74.8 (67.3-82.3)	0.045	
3	76.8 (69.5-84.1)	0.658	
4	76.6 (69.3-83.8)	0.767	
Comparisons between models			
0-1			0.01
1-2			0.003
2-3			0.02
3-4			0.414

*Model 0: FPG; Model 1 (clinical data): family history, FPG, age and sex; Model 2 (the MeS model): all risk factors in Model 1 plus TG, HDL-C, BMI, SBP and DBP; Model 3 (insulin was added for evaluating the effect of insulin level on the model): all risk factors in Model 2 plus FPI; Model 4 (HOMA-IR was added): all risk factors in Model 3, plus HOMA-IR.

***P* values calculated by using the Hosmer-Lemeshow goodness-of-fit test.

****P* values for test of difference in areas under two ROC curves; calculated by the likelihood ratio test.

model, a larger area under the ROC curve could be obtained. In other words, we improved the prediction rate of the models. However, no significant difference was noted between Model 3 and Model 4, implying that adding the parameter HOMA-IR into Model 3 does not further increase the area under ROC curve.

The different ROC curves are shown in Figure 1 panel B. The arrow indicates the arbitrarily selected risk score cutoff (0.39) of Model 3, which has a sensitivity and specificity of 70.1% and 73.6%, respectively, with the area under ROC curve of 76.8% (95% CI, 69.5-84.1%).

DISCUSSION

This is the first study to examine the performance of a simple multivariable risk score model using routinely collected data related to MeS as a screening tool for undetected glucose intolerance in Taiwanese persons. Persons with normal FPG may be considered "non-diabetic". However, several studies have reported that up to half of diabetics are undiagnosed.[8-10,36] Compared to diabetes, IGT is even more difficult to diagnose since OGTT is not routinely done.[37] Although IGT is generally recognized as a "pre-diabetic" state, it still carries an increased risk for developing cardiovascular complications similar to diabetes.[38-40] Therefore, in practice, to identify individuals with dysglycemia it is important for clinicians so that preventive interventions can be given early.

OGTT is costly, time consuming, inconvenient and rarely used in an ordinary clinical setting, but it can identify a subject with normal FPG who may have glucose intolerance (e.g. IGT and DM-on-IPH). Therefore, there is a need to develop a widely accepted method for identifying subjects at high risk for glucose intolerance so that early intervention with lifestyle and/or pharmacologic management can be implemented to prevent or delay diabetes.[41-43]

In our study, we proposed five models with multiple variables related to the components of the MeS, with Model 0, the baseline model, including FPG only. All five models (Figure 1, panel B), including Model 0, were statistically significant ($P<0.05$) meaning that all models for prediction would improve diagnostic performance. We did not use WC in our study because we did not measure it at that time. Although waist circumference is suggested by NCEP ATP III as a tool to define adiposity, its superiority can be questioned.[30] First, Ford et al[44] showed that the correlation coefficient between WC and BMI is high, up to 0.88 in different sex, age or ethnic groups. Secondly, measurement of height and weight is more easily done in a routine clinical setting and is more accurate than measurement of WC. Indeed, there were many different methods to measure WC, each of which would yield various absolute values.[45] Thirdly, one study using the measurement of insulin-mediated glucose disposal has demonstrated a similar relationship between insulin resistance and adiposity, regardless of whether assessed by BMI or WC.[46] Finally, both BMI and WC have been shown to be closely related to the cardiovascular risk factors in Taiwanese persons.[47] For these reasons, we could justify the use of BMI instead of WC in our study and we believe that the findings are not substantially altered.

From the ROC curve of Model 1, the optimum cutoff point we arbitrarily selected was 5.43 mmol/L for FPG, which is less than the ADA criteria (5.6 mmol/L). This yields a sensitivity and specificity of 55.2% and 81.1%, respectively. Interestingly, the predictive discrimination of all of the other multivariable models outperforms Model 0. That is, each of the areas under ROC curves of Model 1 to 4 was greater than the area under the ROC curve of Model 0. The most significant increment in the area was noted between Model 1 and Model 2 (67.3% to 74.8%). This implies that adding components of MeS into the model will significantly increase the predictive discrimination power.

HOMA-IR is an important quantitative method for

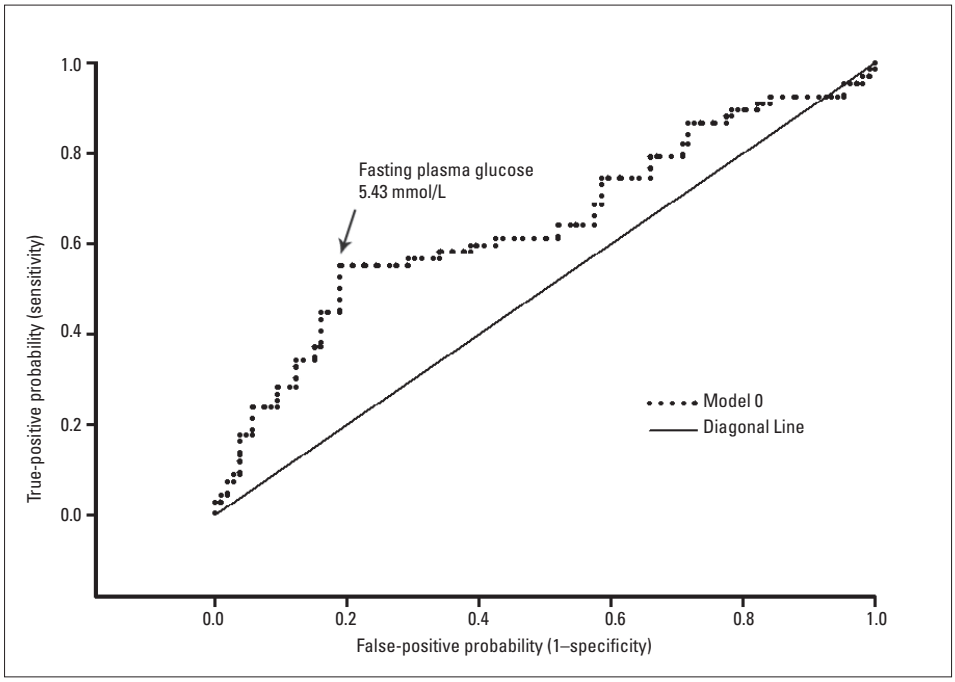

Figure 1A. Receiver operating characteristic curve of Model 0 (see methods for a description of the model). The optimum cutoff (5.43 mmol/L) is shown with an arrow (sensitivity: 55.2%, specificity: 81.1%; area: 67.3%).

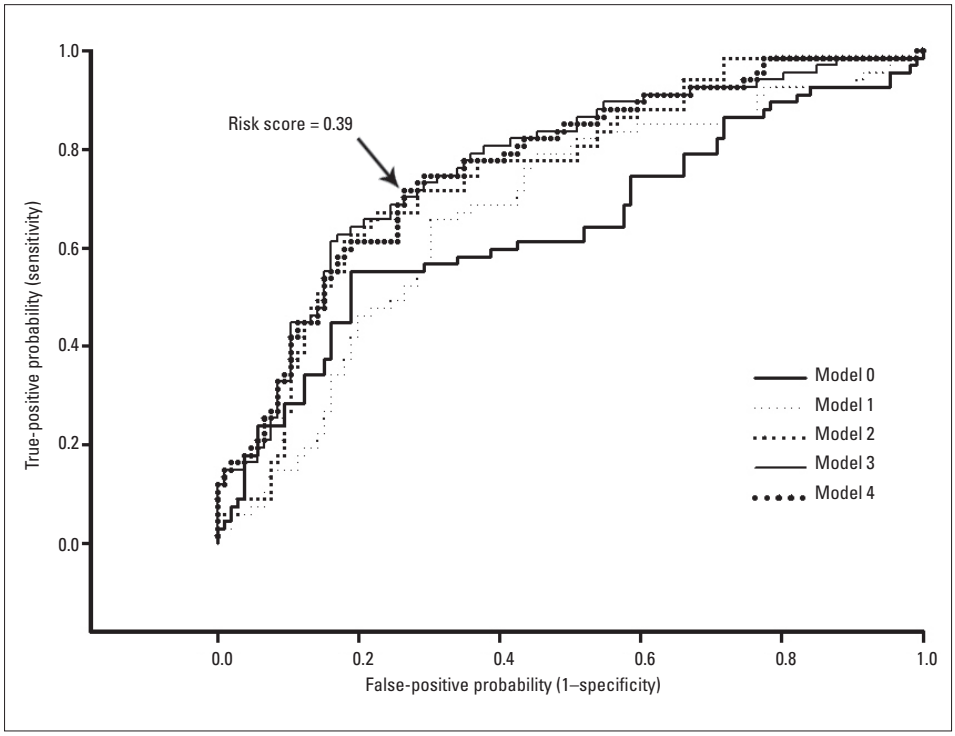

Figure 1B. Receiver operating characteristic curves of the five models, Models 0-4 (see METHODS for a description of the models). The arrow indicates the arbitrarily selected risk score cutoff (0.39) of Model 3 (sensitivity, 70.1%; specificity, 73.6%; area, 76.8%).

the measurement of insulin resistance.[32] In our study, no significant change in the area under the ROC curve was noted after adding the parameter of HOMA-IR into Model 4. This is not surprising because the HOMA-IR is derived from a simple equation multiplying FPI and FPG. Since Model 3 has both of FPI and FPG, Model 4 with HOMA-IR should not be significantly different from Model 3.

Although putting the FPI level into Model 3 will further increase the area under the ROC curve up to 76.8%, it should be noted that FPI is not routinely measured in a routine health check-up. Additionally, the cost is also too high. Thus, considering that there is no significant difference between Model 2 and Model 3 in performance and the simplicity of Model 2, Model 2 seems to be the most appropriate predictive model to be used in the current clinical and health care settings. Nevertheless, it should be noted that Model 3 has the largest area under the ROC curve. The cutoff will vary depending on workload and attitudes to false positives and false negatives. In Model 3, a cutoff of the risk score of 0.39 is suggested, which gives a sensitivity and specificity of 70.1% and 73.6%, respectively, with the area under the ROC curve of 76.8% (95% CI, 69.5-84.1%).

Although many other screening tools for undiagnosed diabetes have also been developed in earlier studies, our study specifically attempts to focus on those persons with normal FPG and evaluates their chance of developing glucose intolerance (dysglycemia). The Herman et al[48] study was the first one that tried to prospectively identify individuals at increased risk for diabetes by using a simple questionnaire. They proposed a classification tree incorporating age, sex, history of delivery of a macrosomic infant, obesity, sedentary lifestyle, and family history of diabetes. In their study, the sensitivity was 79% and the specificity was 65%, which were somewhat better than our model. This might be due to some of the risk factors used in their tree model being not included in our models. In this study, our main purpose was to develop a simple multivariable model consisting of readily available clinical measurements, especially related to the MeS, most of which are routinely obtained anyway. Therefore, we did not put parameters such as macrosomic infant and sedentary lifestyle into our models because they are not routinely collected in the clinical setting. Also, in their study, they tried to identify diabetes, which represents more severe abnormal glucose tolerance than IGT in our study. When a larger range of the risk factors (in this case, blood glucose) are put into the model, the sensitivity and specificity are more accurate and the area under ROC curve larger.

Griffin et al[49] developed the Cambridge risk score, another means of determining risk of diabetes. Other than common risk factors (age, gender, BMI), they considered a history of smoking, and steroid and antihypertensive medication use as risk factors. This model yielded an area under ROC curve of 80%. In another study done by Park et al[50] with the same model, the area under the ROC curve was 65.7%. However, steroid use is not a common condition in Taiwan and, again, this history is not available in a routine health check-up. Therefore, we did not put this risk factor into our model. Although the area under the ROC curve in our Model 2 (74.8%) did not have as good a performance as in the Griffin's study,[49] it is better than the Park study.[50]

Of all the literature reviewed, Stern's model[25] was most similar to ours. In their study, the full model had the same risk factors as our model except for TC, low-density lipoprotein cholesterol (LDL-C), 2-h PG and sibling history. Their prediction model had an area under the ROC curve of around 85%, which is higher than that of our model. The area under the ROC curve in other similar studies using different models ranged from 67% to 80%.[49,51,52] In the above comparisons, our model has also a relatively better performance in sensitivity and specificity. Since most general practical clinics have been computerized, it would be convenient to identify persons with a positive score on Model 2 or 3 with the assistance of a personal computer.

Our study has some limitations. We have to stress that the case cohort in our study was not selected independently and randomly and the population size was also relatively small. Therefore, further randomized and prospective larger-scale studies are needed to validate our predictive model. Nevertheless, to the best of our knowledge, our study is the first one to suggest that using an MeS-related multivariable model could predict subjects with glucose intolerance, including IGT. We hope our study can stimulate the initiation of a larger population-based study.

In conclusion, we have demonstrated that the predictive performance of Model 2 and 3 using the components of the MeS, which are routinely available data, and FPI is significantly better than FPG and/or family history alone. Without much effort, subjects with normal FPG at high risk for glucose intolerance could be identified early in the clinical setting, and then followed by the 75-g OGTT for further diagnosis. We hope that our predictive model can be validated by a large-scale longitudinal cohort study in the future and accepted widely by general practitioners.

Appendix:

The following are parameter estimates for the Model 3 in this study:

$p=1/(1+e^{-X})$, where X=-7.094+0.132(FPG)+0.242(sex)−0.091(FH)+0.039(age)+0.07(BMI)+0.014(SBP)−0.001(DBP)+0.474(TG)−0.116(HDL-C)+0.008(FPI). In this equation, *p*, the probability of developing diabetes; FPG, fasting plasma glucose in mmol/L; sex=1 if female, 0 if male; FH=0 if no parents have diabetes, 1 if one of the parents has diabetes; age is in years; BMI, body mass index in kg/m^2; SBP, systolic blood pressure in mm Hg; DBP, diastolic blood pressure in mm Hg; TG, triglycerides in mmol/L; HDL-C, high-density lipoprotein cholesterol in mmol/L; FPI, fasting plasma insulin in pmol/L.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of diabetes: Estimates for the year 2000 and projections for 2030 Diabetes Care 2004;27:1047-53.

2. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414:782-7.

3. Harris MI, Klein R, Wellborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. Diabetes Care 1992;15:815-9.

4. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990;263:2893-8.

5. UK Prospective Diabetes Study Group. UK prospective diabetes study 6. Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. Diabetes Res Clin Pract 1990;13:1-11.

6. The DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. Lancet 1999;354:617-21.

7. DECODE Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;l61:397-405.

8. Charles MA, Balkau B. Revision of diagnostic criteria for diabetes (Letter). Lancet 1996;348:1657-8.

9. Stolk RP, Pols HA, Lamberts SW, de Jong PT, Hofman A, Grobbee DE. Diabetes mellitus, impaired glucose tolerance and hyperinsulinemia in an elderly population:the Rotterdam study. Am J Epidemiol 1997;145:24-32.

10. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Heine RJ. Prevalence and determinants of glucose intolerance in a Caucasian population: the Hoorn Study. Diabetes Care 1995;18:1270-3.

11. Balkau B, Eschwège E. The diagnosis and classification of diabetes and impaired glucose regulation:In Pickup JC and Williams G (ed.). Textbook of Diabetes. 3rd edition. London: Blackwell, 2002;2.1-2.13.

12. Chang CJ, Lu FH, Yang YC, Wu JS, Wu TJ, Chen MS, et al. Epidemiology study of type 2 diabetes in Taiwan. Diabetes Res Clin Pract 2000;50(Suppl 2): S49-59.

13. Tai TY. Current status of diabetes in Taiwan. Diabetes Res Clin Pract 2000;50(Suppl 2):S1-2.

14. Taiwan Area Main Causes of Death (2002). Table 1- main causes of death in Taiwan, Department of Health, Taiwan, R.O.C. [cited 29 Aug 2005]. Available from http://www.doh.gov.tw/ufile/Doc/S02/9101-eng.xls

15. Lin RS, Lee WC. Trends in mortality from diabetes mellitus in Taiwan, 1960-1988. Diabetologia 1992;35:973-9.

16. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report on the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997;20:1183-97.

17. Alberti KGGM, Zimmet PA for the WHO Consultation. Definition, diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. Diabet Med 1998;15:539-53.

18. de Vegt F, Dekker JM, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. The 1997 American Diabetes Association criteria versus the 1985 World Health Organization criteria for the diagnosis of abnormal glucose tolerance. Poor agreement in the Hoorn study. Diabetes Care 1998;21:1686-90.

19. Gimeno SG, Ferreira SR, Franco LJ, Iunes M. Comparison of glucose tolerance categories according to World Health Organization and American Diabetes Association diagnostic criteria in a population-based study in Brazil. The Japanese-Brazilian Diabetes Study Group. Diabetes Care 1998;21:1889-92.

20. Gomez-Perez FJ, Aguilar-Salinas CA, Lopez-Alvarenga JC, Perez-Jauregui J, Guillen-Pineda LE, Rull JA. Lack of agreement between the World Health Organization catergory of impaired glucose tolerance and the American Diabetes Association category of impaired fasting glucose. Diabetes Care 1998:21:1886-8.

21. Richard JL, Vannereau D, Parer-Richard C. Impact of new ADA diagnostic criteria for diabetes on an obese population: Comparison with OGTT-based WHO criteria. Preliminary results. Diabetes Metab 1998;24:365-7.

22. Wahl PW, Savage PJ, Psaty BM, Orchard TJ, Robbins JA, Tracy RP. Diabetes in older adults: comparison of 1997 American Diabetes Association classification of diabetes mellitus with 1985 WHO classification. Lancet 1998;352:1012-5.

23. Lindahl B, Weinehall L, Asplund K, Hallmans G. Screening for impaired glucose toterance. Results form a population-based study in 21,057 individuals. Diabetes Care 1999;22:1988-92.

24. Harris MI. Undiagnosed NIDDM: clinical and public health issues. Diabetes Care 1993;16:642-53.

25. Stern MP, Williams K, Haffner SM. Identification of persons at high risk for type 2 diabetes mellitus: Do we need the oral glucose tolerance test? Ann Intern Med 2002;136:575-81.

26. Zimmet PZ, Collins VR, Dowse GK, Knight LT. Hyperinsulinaemia in youth is a predictor of type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1992;35:534-41.

27. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 1992;41:715-22.

28. Stern MP. Glycemia and cardiovascular risk. Diabetes Care 1997;20:1501-2.

29. Reaven GM. Role of insulin resistance in human disease. Diabetes Care 1988;37:1595-607.

30. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

31. 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

32. 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.

33. Emoto M, Nishizawa Y, Maekawa K. Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetes patients treated with sulfonylureas. Diabetes Care 1999;22:818-22.

34. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462-70.

35. Shen SW, Reaven GM, Farquhar JW. Comparison of impedance to insulin-mediated glucose uptake in normal subjects and in subjects with latent diabetes. J Clin Invest 1970;49:2151-60

36. King H, Rewer M. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. Diabetes Care 1993;16:157-77.

37. Abate N. Insulin resistance and obesity: the role of fat distribution pattern. Diabetes Care 1996;19:292-4.

38. Ceriello A. Impaired glucose tolerance and cardiovascular disease: the possible role of postprandial hyperglycemia. Am Heart J 2004;147:803-7.

39. Baron AD. Impaired glucose tolerance as a disease. Am J Cardiol 2001;88(6A):16H-19H.

40. Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular complications of impaired glucose tolerance. Diabetes 2003;52:2867-73.

41. Pan X, Li G, Hu Y, Wang J, Yang W, An Z et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT Diabetes Study. Diabetes Care 1997;20:537-44.

42. Tuomilehto J, Lindstrom J, Eriksson J, Valle T, Hamalainen H, Ilanne-Parikka P et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-50.

43. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.

44. Ford ES, Mokdad AH, Giles WH. Trends in waist circumference among U.S. adults. Obes Res 2003;11:1223-31.
45. Wang J, Thornton JC, Bari S, Wiliamson B, Gallagher D, Heymsfield SB, et al. Comparisons of waist circumferences measured at 4 sites. Am J Clin Nutr 2003;77:379-84.
46. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G. Insulin Resistance and Hypersecretion in Obesity:the European Group for the Study of Insulin Resistance (EGIR). J Clin Invest 1997;100:1166-73.
47. Huang KC, Lin WY, Lee LT, Chen CY, Lo H, Hsia HH et al. Four anthropometric indices and cardiovascular risk factors in Taiwan. Int J Obes Relat Metab Disord 2002;26:1060-8.
48. Herman WH, Smith PJ, Thompson TJ, Engelgau MM, Aubert RE. A new and simple questionnaire to identify people at increased risk for undiagnosed diabetes. Diabetes Care 1995;18:382-7.
49. Griffin SJ, Little PS, Hales CN, Kinmonth AL, Wareham NJ. Diabetes risk score: towards earlier detection of type 2 diabetes in general practice. Diabetes Metab Res Rev 2000;16:164-71.
50. Park PJ, Griffin SJ, Sargeant L, Wareham NJ. The performance of a risk score in predicting undiagnosed hyperglycemia. Diabetes Care 2002;25:984-8.
51. Baan CA, Ruige JB, Stolk RP, Witteman JC, Dekker JM, Heine RJ, Feskens EJ. Performance of a predicitive model to undiagnosed diabetes in a health care setting. Diabetes Care 1999;22:213-9.
52. Spijkerman AMW, Yuyun MF, Griffin SJ, Dekker JM, Nijpels G, Wareham NJ. The Performance of a risk score as a screening test for undiagnosed hyperglycemia in ethnic minority groups: Data from the 1999 health survey for England. Diabetes Care 2004;27:123-8.