The performance of risk scores and hemoglobin A1c to find undiagnosed diabetes with isolated postload hyperglycemia

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Abstract. The aim of this study is to develop strategies to screen diabetic subjects with isolated postload hyperglycemia (IPH) in Chinese population. We included 1175 adult subjects who did not report diabetes were included. Diabetes was diagnosed by oral glucose tolerance tests. IPH was defined as fasting plasma glucose (FPG)<7 mmol/L and 2-hour post-load plasma glucose (2hPG) greater than 11.1 mmol/L. Using FPG criteria, only 59.8% of diabetic subjects were not identified, showing a poor agreement between FPG and 2hPG criteria (kappa 0.294). Age, FPG, total cholesterol, triglycerides, blood pressure, body mass index, HbA1c and medication for hypertension were associated factors for IPH. Four scores were constructed using all these factors, age and blood test results, age and HbA1c, and data from non-invasive examinations, respectively. The area under the ROC curve were 0.9296(*95%CI* 0.8948-0.9643), 0.9111(*95%CI* 0.8713-0.9508), 0.8902(*95%CI* 0.8341-0.9646), 0.8924(*95%CI* 0.7835-0.8753), and 0.8654(*95%CI* 0.7963-0.9345) for score 1, 2, 3, 4, and HbA1c, respectively. The sensitivity of all four risk scores to detect IPH was better than that of impaired fasting glucose (IFG). The sensitivity and specificity of HbA1c at cutoff 6.2% for detecting IPH was also better than that of IFG. In conclusion, the risk scores and HbA1c are useful to identify subjects with undiagnosed IPH, with better performance than IFG.

Key words: Isolated postload hyperglycemia, Risk score, Impaired fasting glucose

RECENTLY, type 2 diabetes mellitus (DM) become pandemic as a result of aging, change in lifestyle, and obesity. In 2000, people with DM were estimated to be 171 million. Within 30 years, people with DM are predicted to double, to become 366 million in 2030 [1]. A significant proportion of people with DM are asymptomatic and undiagnosed, who are often identified after complications have developed [2]. These impose a heavy burden on personal and public health.

Early detection of DM may improve health outcome through prompt health intervention. Screening for DM

is therefore suggested under certain circumstances. Many reports developed risk scores to identify subjects with undiagnosed DM to receive standard 75-gram oral glucose tolerance test (OGTT) [3-8]. The European Association for the Study of Diabetes and the European Society of Cardiology recommended that primary screening should be done by non-invasive risk scores followed by confirmatory OGTT [9]. The American Diabetes Association (ADA) suggested that subjects older than 45 years or subjects with obesity plus an additional risk factor should be screened for diabetes, by either fasting plasma glucose (FPG) tests or OGTT[10]. Although OGTT is gold standard to diagnose DM, measuring FPG is preferred in clinical settings because it is easier to perform, more convenient for subjects being examined, and less expensive than OGTT. Therefore, FPG test is recommended by the

World Health Organization (WHO) and the International Diabetes Federation (IDF) [11, 12]. Previous studies have demonstrated that hemoglobin A1c (HbA1c) was an alternative screening tool for detecting DM [13, 14]. In Taiwan, the National Health Insurance Program, implemented since March 1995 to cover over 96% of Taiwanese population [15], routinely offers health examination at 3-year intervals beginning at age 40 years for whole population. Fasting plasma glucose (FPG) was used to detect DM in this program.

Many reports have shown that the agreement was low between screening diabetes by FPG tests and OGTT [16-20]. There was high prevalence of diabetes with isolated postload hyperglycemia (IPH) (FPG<7 mmol/L and 2-hour-postload glucose, 2hPG, ≥11.1 mmol/L), especially in the elderly [19]. In other words, subjects with IPH will not be diagnosed correctly by FPG test only, if subsequent OGTT is not done. Therefore, the WHO suggested that subjects with impaired fasting glucose (IFG), i.e. FPG 6.1-6.9 mmol/L, should have an OGTT if resources allowed [12]. The ADA and IDF have similar recommendation with a modification of the IFG definition to be FPG 5.6-6.9 mmol/L [10, 11]. To our best knowledge, there is no report evaluating the performance of IFG in screening subjects with IPH. There was a report demonstrating that using FPG to find subjects with 2hPG ≥11.1 mmol/L is specific but is not sensitive [20]. They also found that the optimal FPG cutoff was influenced by age, gender, body mass index (BMI), and the presence of hypertension.

Therefore, the aim of the present study is to develop a strategy to find subjects with IPH. Simple risk scores were constructed by important risk factors of IPH, including age, BMI, hypertension, and/or data from blood tests. The performance of these risk scores, HbA1c and IFG in screening subjects with IPH was compared.

Materials and Methods

Subjects

During 2006-2009, subjects aged 20 years and above, who did not report diabetes during the interview, were invited to participate in this study (Taiwan Lifestyle Study) [21, 22]. Written informed consent was obtained from each individual, and the study was reviewed and approved by the Institutional Review Board.

Methods

Body height and weight were recorded to the nearest 0.5cm and 0.1 kg, respectively. BMI was derived from body weight in kilogram divided by the square of body height in meters. Waist and hip circumferences were measured in standard way to the nearest 0.1cm. Waist to hip ratio (WHR) was calculated by divided waist by hip circumference. Blood pressure was recorded by a mercury sphygmomanometer to the nearest 2 mm-Hg with the arm supported at heart level after sitting quietly for 10 minutes. Trained nurses took three separate readings at 1-minute intervals. The average of the second and the third readings was used for analysis. A standard 75-gram OGTT was performed for measurements of fasting and 2hPG after fasting at least 8 hours.

Plasma glucose and fasting serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) were measured with an automatic analyzer (Toshiba TBA 200 FR, Toshiba Medical Systems Co., Ltd., Tokyo, Japan). LDL-C was measured directly by enzymatic assay (Denka Seiken Co. Ltd, Tokyo, Japan). Briefly, after elimination of chylomicron, very-low-density lipoprotein cholesterol, and HDL-C, LDL-C was determined by chemical reactions catalyzed by cholesterol esterase, cholesterol oxidase, and peroxidase, followed by measuring quinine pigment photometrically.

Definitions

Normal (FPG<5.5 mmol/L and 2hPG<7.8 mmol/L), IFG (FPG 5.6-6.9 mmol/L), IFG and/or impaired glucose tolerace (IGT) (FPG 5.6-6.9 mmol/L and/or 2hPG 7.8-11.0 mmol/L) and DM (FPG ≥7 mmol/L and/or 2hPG ≥11.1 mmol/L) were diagnosed and classified according to criteria of the ADA [23] and WHO [12] by the results from OGTT. IPH was defined as FPG <7 mmol/L and 2hPG ≥11.1 mmol/L.

Hypertension was defined if the systolic blood pressure was higher than 140 mmHg, or the diastolic blood pressure was greater than 90 mmHg, or the subject was taking medication for hypertension. Family history of DM was defined that parents, grandparents or sibling had diabetes.

Statistical analysis

Data were presented as the mean and standard deviation (SD) for continuous variables, and as a percentage for categorical variables. One-way analysis

Table 1 Comparison of FPG and OGTT 2-hour postload glucose (2hPG) diagnostic categories for those without reported diabetes.

	FPG, mmol/L			Total	Prevalence by 2hPG, %
	< 5.5	5.6-6.9	≥7		
2hPG, mmol/L					
<7.8	817(82.6)	72(47.1)	1(3.0)	890	75.8
7.8-11.0	156(15.8)	48(31.4)	2(6.1)	206	17.5
≥11.1	16(1.6)	33(21.6)	30(90.9)	79	6.7
Total	989	153	33	1175	100
Prevalence by FPG, %	84.2	13.0	2.8	100	-

( ), percentage (%) in the same FPG diagnostic category

of variance (ANOVA) and chi-square tests were used to identify the differences in various demographic and metabolic characteristics among normal, IFG and/or IGT, and DM. The Bonferroni method was used for post-hoc comparisons in ANOVA. The weighted kappa statistic was used for the degree of agreement between FPG and 2hPG to diagnose diabetes.

Odds ratios (OR) and the 95% confidence intervals (CI) for IPH were derived from univariate and multivariate logistic regression models, using subjects with FPG <7 mmol/L and 2hPG <11.1 mmol/L as the reference group (OR=1). Multivariate logistic regression was performed to construct models for IPH. These models were used to construct risk scores, defined as followed.

Risk score = $\beta_1 X_1 + \beta_2 X_2 + \ldots\ldots + \beta_n X_n$

$\beta_1 \ldots\ldots \beta_n$: logistic regression coefficient

$X_1 \ldots\ldots X_n$: variable

Subsequently, we evaluate the performance of the risk scores by calculating the area under the Receiver-Operator curve (ROC curve) as a measure of diagnosis accuracy. Optimal cutoff point was derived from the ROC curve with shortest distance to sensitivity =1 and 1-specificity =0. The sensitivity of a risk score is the probability that the prediction is positive for subjects with IPH. The specificity of a risk score is the probability that the prediction is negative for subjects without IPH. The performance of IFG and HbA1c for detecting IPH were also calculated.

A *p*-value below 0.05 was considered significant. The statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL) and Stata/SE 9.0 for Windows (StataCorp LP, Texas).

Results

A total of 1175 subjects, aged 20-88 years, including 452 males and 723 females, were included in this study. Table 1 showed the distribution of people according to FPG and 2hPG diagnostic criteria. Of the 1175 participants, 33 subjects (2.8%) were diagnosed as DM according to results from FPG tests; while 79 subjects (6.7%) had DM according to results from 2hPG criteria. There were 82 subjects with DM based on the results of OGTT. Among them, only 40.2% (33 subjects) were diagnosed correctly by FPG tests. In other words, to diagnose DM by FPG test missed 59.8% (49 subjects) of people with DM in this population. Among subjects with FPG <5.5, 5.6-6.9, and ≥7 mmol/L, the percentages of subjects diagnosed as DM by 2hPG ≥11.1 mmol/L are 1.6%, 21.6%, and 90.9%, respectively. The agreement between criteria to diagnose DM by FPG and 2hPG was not good, with the kappa statistic 0.294 (*95%CI* 0.235-0.353).

Table 2 shows the demographic and biochemical characteristics among subjects with normal, IFG and/or IGT, and DM. Subjects with diabetes were older and had a higher HbA1c, BMI, waist-to-hip ratio, SBP, hypertension rate, TC and TG than subjects with normal glycemia in both sexes. Similar trend was observed between subjects with normal glycemia and IFG and/or IGT. There were 22 subjects (1.9%) who were taking medications for dyslipidemia. The percentages of subjects who were taking medications for dyslipidemia were not statistically different among subjects with euglycemia, IFG and/or IGT, and diabetes.

There were 1142 subjects whose FPG were less than 7 mmol/L, including 49 subjects with IPH. Their data were used to assess the associated factors of IPH. As shown in Table 3, age, FPG, TC, TG, SBP, DBP, BMI, HbA1c and medication for hypertension were associated factors for IPH. Four models were constructed. In model 1 (full model), age, FPG, TG, BMI and HbA1c remained to be significant related factors after controlling other factors. In model 2 (blood test model), age, FPG and TG were significant after other factors were adjusted. In model 3, HbA1c was strong associated with detecting IPH after adjusting

Table 2 Demographic and biochemical characteristics among subjects with normal glycemia, impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), and DM.

Variables	Male			Female		
	Normal	IFG and/or IGT	DM	Normal	IFG and/or IGT	DM
Number	305	111	36	512	165	46
Age, year	48.9±14.4	57.3±11.9‡	59.4±11.1†¶	45.8±12.4	53.6±10.8‡	58.3±10.4†¶
FPG, mmol/L	4.9±0.3	5.5±0.5‡	6.8±1.6†¶	4.8±0.3	5.3±0.5‡	7.5±2.9†¶
2hPG, mmol/L	5.5±1.2	8.1±1.6‡	14.4±2.4†¶	5.7±1.1	8.3±1.4‡	15.0±5.6†¶
HbA1c, %	5.6±0.4	5.8±0.4‡	7.0±1.0†¶	5.5±0.4	5.8±0.4‡	7.6±2.3†¶
BMI, kg/m²	24.5±3.5	25.4±3.1	26.4±2.7†	23.3±4.1	24.6±3.4‡	26.8±4.3†¶
Waist-to-hip ratio	0.92±0.06	0.94±0.06‡	0.96±0.06†	0.87±0.07	0.90±0.07‡	0.94±0.07†¶
SBP, mmHg	126±15	135±18‡	136±15†	116±16	126±16‡	132±18†
DBP, mmHg	81±10	86±11‡	83±10	75±11	80±9‡	82±10†¶
Use of medication for hypertension, %	14.1	27.0‡	22.2	8.2	21.8‡	30.4†
Hypertension, %	29.2	51.4‡	50.0†	15.8	35.8‡	45.7†
Family history of DM, %	35.1	24.3	27.8	36.7	35.8	26.1
TC, mg/dL	189±37	196±32	207±35†	191±35	204±40‡	218±41†¶
HDL-C, mg/dL	46.8±11.3	45.8±9.4	46.6±14.3	56.1±12.8	52.9±12.5‡	52.4±10.4
LDL-C, mg/dL	119±33	124±33	130±34	113±36	126±38‡	134±38†
TG, mg/dL	124±79	149±97‡	167±81†	86±45	121±63‡	153±84†¶
Use of medication for dyslipidemia, %	1.7	4.6	5.6	1.0	3.0	0

†indicates a significant difference (*p*<0.05) between normal and DM by ANOVA with post-hoc comparison for male and female separately. ‡ indicates a significant difference (*p*<0.05) between normal and IFG and/or IGT by ANOVA with post-hoc comparison for male and female separately. ¶ indicates a significant difference (*p*<0.05) between IFG and/or IGT and DM by ANOVA with post-hoc comparison for male and female separately. BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 3 Univariate and multivariate logistic regression analyses for factors associated with IPH.

variable	Univariate analysis OR(*95% CI*)†	Model 1 OR(*95% CI*)‡	Model 2 OR(*95% CI*)‡	Model 3 OR(*95% CI*)‡	Model 4 OR(*95% CI*)‡
Number, diabetes/non-diabetes	49/1093	49/1093	49/1093	49/1093	49/1093
Age	1.08* (1.06-1.11)	1.06* (1.02-1.11)	1.08* (1.05-1.12)	1.05* (1.01-1.08)	1.08* (1.05-1.11)
Sex					
Male	1.70 (0.96-3.01)				
Female	1				
FPG, mmol/L	15.5* (8.80-27.2)	4.73* (2.26-9.90)	12.3* (6.69-22.6)		
TC, mmol/L	1.69* (1.27-2.23)	1.20 (0.81-1.76)	1.33 (0.94-1.89)		
TG, mmol/L	1.51* (1.26-1.80)	1.48* (1.12-1.94)	1.59* (1.25-2.02)		
SBP	1.04* (1.02-1.05)	1.01 (0.99-1.04)			1.02*(1.00-1.04)
DBP	1.04*(1.01-1.06)				
BMI, mg/m²	1.15* (1.06-1.24)	1.11* (1.03-1.19)			1.14* (1.05-1.22)
Medication for hypertension					
No	1	1			1
Yes	2.25* (1.17-4.35)	0.99 (0.41-2.42)			0.79 (0.38-1.22)
Family history of DM					
No	1				
Yes	0.48* (0.24-0.97)				
Use of alcohol					
No	1				
Yes	1.01(0.50-2.06)				
Smoking					
No	1				
Yes	1.21 (0.61-2.41)				
HbA1c	39.2*(18.7-82.3)	8.60*(3.67-20.1)		29.7* (13.9-63.4)	

* *p*<0.05 † : odds ratio by univariate logistic regression. ‡ : odds ratio by multivariate logistic regression. 2hPG, 2-hour postload plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.
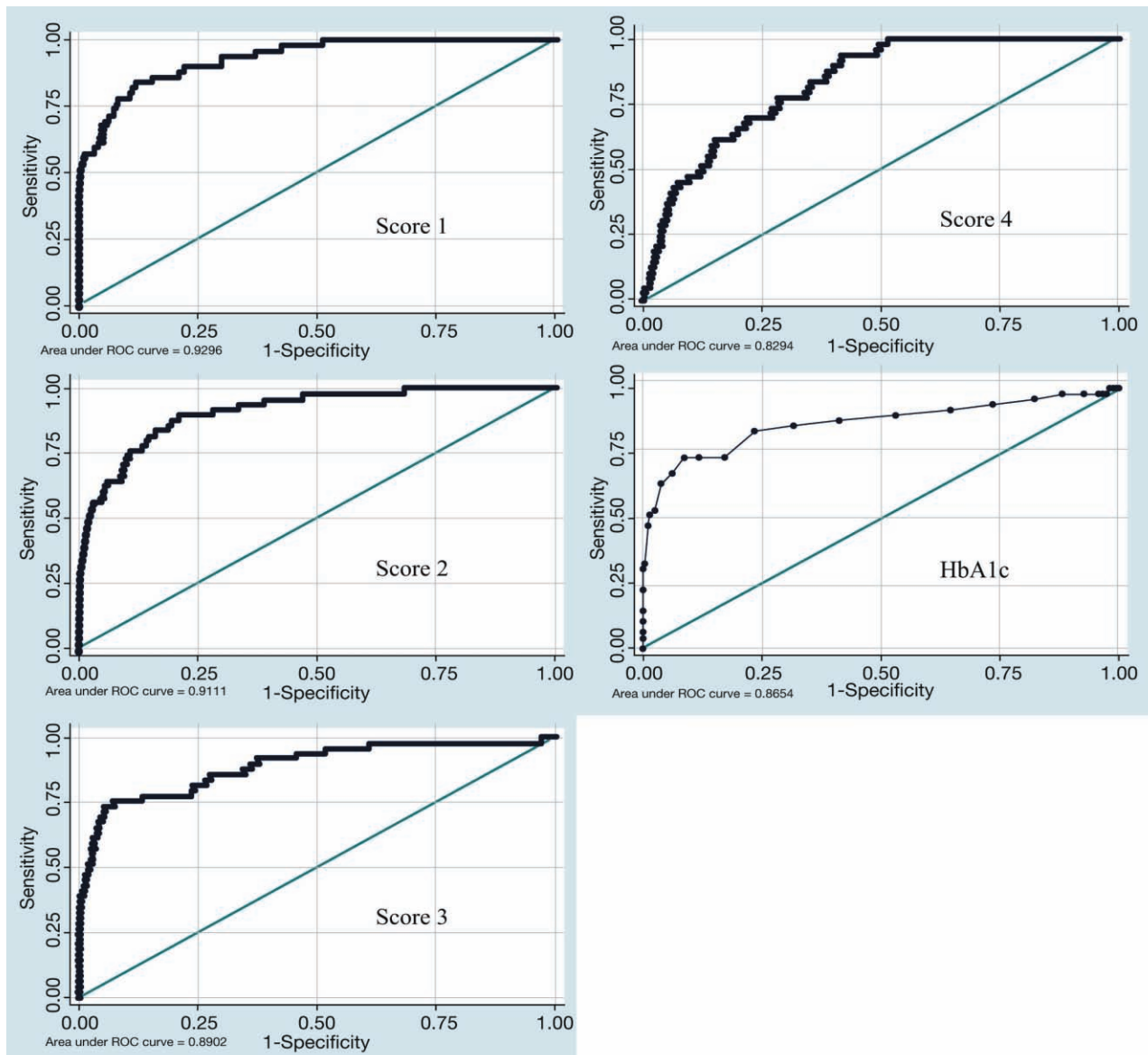
Fig. 1 ROC curve of risk scores and HbA1c in finding subjects with isolated postload hyperglycemia.

age. In model 4 (non-invasive model), age, SBP and BMI remained significant after adjustment.

We constructed fourth risk scores, derived from multivariate logistic models in table 3, for predicting subjects with IPH. The risk scores were described as followed.

Score 1: DM=0.062×Age (year)+1.555×FPG(mmol/L)
+ 0.178×TC (mmol/L)+ 0.389×TG(mmol/L)
+ 0.013×SBP (mm-Hg) + 0.104×BMI(kg/m^2)
- 0.008 if use of drugs for hypertension +
2.151×HbA1c(%)

Score 2: DM=0.081×Age + 2.508×FPG + 0.285×TC +
0.462×TG

Score 3: DM=0.047×Age + 3.390×HbA1c

Score 4: DM=0.074×Age + 0.020×SBP + 0.126×BMI
- 0.238 if use of drugs for hypertension

The area under the ROC curve (AUC) of score 1, 2, 3, 4 and HbA1c were 0.9296 (*95%CI* 0.8948-0.9643), 0.9111 (*95%CI* 0.8713-0.9508), 0.8902 (*95%CI* 0.8341-0.9464), 0.8294 (*95%CI* 0.7835-0.8753), and 0.8654 (0.7963-0.9345), respectively (Table 4 and Fig. 1). As shown in Table 4, sensitivity of these four scores and HbA1c were higher than the sensitivity of IFG, both defined by FPG 5.6-6.9 mmol/L and defined by FPG 6.1-6.9 mmol/L. The specificity for score 1, 2, 3, 4 and HbA1c were 88.4%, 83.7%, 92.7%, 71.4%, and 91.3%.

Table 4 Comparison of different scores and criteria used to screen isolated postload hyperglycemia.

	AUC of ROC (*95% CI*)	Optimal cutoff	Sensitivity (%)	Specificity (%)
Score 1	0.9296 (0.8948-0.9643)	31.14	83.7	88.4
Score 2	0.9111 (0.8713-0.9508)	20.54	83.7	83.7
Score 3	0.8902 (0.8341-0.9464)	23.80	75.5	92.7
Score 4	0.8294 (0.7835-0.8753)	9.84	77.6	71.4
A1c	0.8654 (0.7963-0.9345)	6.2	73.5	91.3
IFG (FPG 5.6-6.9 mmol/L)			67.3	89.0
IFG (FPG 6.1-6.9 mmol/L)			38.8	98.1

Discussion

In the present study, we found that the agreement between criteria using FPG and 2hPG to diagnose DM was not good, which was in concordance with previous reports. A total of 59.8% subjects with DM were missed if we used FPG tests only to diagnose DM. Age, FPG, TC, TG, blood pressure, BMI, HbA1c and medication for hypertension were associated risk factors for IPH. The four risk scores and HbA1c had better performance to find subjects with IPH than IFG.

We found that the overall rates of undiagnosed DM were 2.8% according to FPG-based criteria and 6.7% according to 2hPG-based criteria (Table 1). The agreement between the two criteria was not good. In the Strong Heart Study (SHS), they reported a 1.5% more subjects with DM diagnosed by 2hPG than FPG criteria, supporting our findings [16]. Similarly, in the Guía Study (GS), they found a 2.8% difference between the 2 criteria [18]. As shown in Asian population in DECODA study [24] or African population in another study [25], the difference varied when different populations were studied. We also found a significant portion of subjects (4.2%) with undiagnosed DM (IPH) in this population. Using FPG test only, 59.8% of subjects with DM were not identified. A study on Japanese-American men also demonstrated that 66.1% (341/516) of subjects were not identified by FPG tests only [19]. Compared with data from Asian populations, rates of IPH from western countries were lower but still high enough [16-18, 25], 29.0% (154/531) in the SHS [16], 19.7% (27/137) in the GS [18], and 41.1% (125/304) in the Third National Health and Nutrition Examination Survey (NHANES III) [17].

In present study, age was found to be an important risk factor for IPH, which was supported by the findings in NHANES III [17]. Indeed, a study on elderly aged 65-100 years showed a higher prevalence of IPH [26]. Therefore, we strongly suggest that OGTT should be performed to find undiagnosed IPH, especially in elderly populations.

The WHO recommended that those with IFG should have an OGTT to ascertain diabetes [12]. The performance of IFG by WHO, i.e. FPG 6.1-6.9 mmol/L, as a screening test for IPH was poor in our study. The sensitivity and specificity were 38.8% and 98.1%, respectively (Table 4), which was similar to the results reported previously in Asian population [20]. Using modified definition of IFG by ADA and IDF, i.e. FPG 5.6-6.9 mmol/L, the sensitivity and specificity were 67.3% and 89.0%, respectively (Table 4). Apparently, the IFG criterion is a specific but insensitive test for IPH in Chinese population, suggesting that the performance of IFG criterion is not good as a screening tool. These results could be explained biologically and epidemiologically. Biologically, the pathophysiology of IFG is different from impaired glucose tolerance or IPH [27]. Subjects with IFG have severe insulin resistance in liver with normal or near-normal insulin sensitivity in muscle. In contrast, subjects with impaired glucose tolerance or IPH have severe muscle insulin resistance with only mild hepatic insulin resistance. Epidemiologically, as shown in Table 3, 2hPG is not only associated to FPG, but also to age, BMI, HbA1c and the other factors. In this study, the sensitivity and specificity for HbA1c at cutoff 6.2% were 73.5% and 91.3%, respectively, which were both better than IFG. Therefore, HbA1c may be an alternative and simple choice for screening IPH.

Based on the four risk scores constructed in this study, we would like to discuss screening strategy for IPH. Score 4 was calculated by data from non-invasive examinations, such as age, systolic blood pressure, BMI, and medication for hypertension. If one-visit screening strategy is preferred and FPG test only is still considered, score 4 could be used to decide if a subject should receive an OGTT or FPG test only. On the other hand, if sequential screening strategy is preferred, i.e.

FPG test followed by OGTT in separate visits, score 1 and 2 have shown to be useful to have high AUC, sensitivity, and specificity for IPH. Alternatively, if non-fasting, sequential screening strategy is preferred, i.e. non-fasting blood test followed by OGTT in separate visits, score 3 provided a practical way.

Several predictive models for screening undiagnosed DM have been reported [3-6, 8, 28-31]. The ADA suggests some criteria, including BMI, age, ethnic population, history of gestational DM, hypertension etc., to screen for IFG and/or IGT and DM in asymptomatic individuals [28]. A classification tree composed of some risk factors by questionnaire has also been reported with a sensitivity of 79% and specificity of 65% for detecting undiagnosed DM [3]. The latest published models from Chinese population [32-34] and various risk scores from other ethnic population [4-6, 8, 29-31] were all developed to identify people at risk of undetected DM, but not people with IPH. The present study was the first to focus on suggesting effective and practical screening strategies for people with IPH.

In present study, the percentage of family history of DM in subjects with DM was lower, although which was not statistically significant (Table 1). These may result from the consequence of national free screening program in Taiwan. Subjects with family history of DM may have greater motivation to participate the national free screening program. Once DM is found by the screening program, they will be treated at hospital and will not be recruited to our study. Since most of the countries or cities do not have free screening program, the relationship between family history of DM and IPH found in the present study may not be generalized to other countries or cities. Therefore, we did not include family history of DM into the risk scores.

In conclusion, our results showed that the agreement between FPG and 2hPG to diagnose DM was not good and 59.8% subjects with DM were not identified by FPG tests. Subjects with older age, higher FPG, TC, TG, blood pressure, BMI, HbA1c and use of medications for hypertension were associated with IPH. The performance of the four risk scores and HbA1c are better than IFG in identifying subjects with undiagnosed IPH.

Acknowledgments

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