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Fasting Plasma Glucose Cutoff Value for the Prediction of Future Diabetes Development: A Study of Middle-Aged Koreans in a Health Promotion Center

We determined optimal fasting plasma glucose (FPG) cutoff values predictive of future diabetes development in a group of middle-aged Koreans who visited a health promotion center. The medical records of 2,964 subjects, who attended the Health Promotion Center in 1998 and 2003, were examined. Subjects were classified into four groups according to their baseline FPG values (Group 1:FPG <5.0 mM/L; Group 2: 5.0≤FPG <5.6 mM/L; Group 3: 5.6≤FPG <6.1 mM/L; Group 4: 6.1≤FPG <7.0 mM/L). No significant difference was observed between Group 1 and Group 2 in terms of diabetes incidence. However, incidence in Group 3 was significantly higher than that in Group 1 [hazards ratio 4.88 (1.65-14.41), p=0.004] and the hazards ratio in Group 4 for diabetes was 36.91 (13.11-103.61), p<0.001, versus Group 1. Receiver operator characteristics curve analysis showed that an FPG of 5.97 mM/L represents the lower limit and gives the best combination of sensitivity and specificity. Our data shows that the risk of future diabetes development started to increase below an FPG of 6.1 mM/L and suggests the importance of efforts to modify diabetes development risk factors at lower impaired fasting glucose levels.

Key Words : *Diabetes Mellitus; Blood Glucose; Reference Values; Korea*

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INTRODUCTION

Evidence is accumulating that macrovascular disease is associated with lower degrees of hyperglycemia than microvascular disease. And, plasma glucose values have been associated with a risk of future diabetes, cardiovascular disease, and total mortality (1-3). Some studies have suggested that an fasting plasma glucose (FPG) of 5.7 mM/L is a more meaningful cut off than a 2-hr cut-off of 7.8 mM/L in terms of its sensitivity for predicting future diabetes and for defining categories with similar (IGT) prevalences (4, 5). However, determined FPG cutoff values suitable for predicting future diabetes development may be population dependent. Therefore, published findings need to be tested in populations with different environmental and genetic backgrounds.

Asia is expected to experience the greatest increase in diabetes cases over the next two decades. Recently, after investigating the medical records of 54,623 Korean subjects, we reported that FPG levels of <6.10 mM/L are closely related to the frequencies of cardiovascular risk factors including obesity, hypertension, and dyslipidemia (6). In this study, we undertook to investigate the incidence of diabetes after a 5-yr follow-up period versus initial FPG values in a Korean population, and estimated the optimal FPG value predictive of future diabetes.

MATERIALS AND METHODS

Samsung Medical Center is a 1,300-bed hospital and one of the largest referral centers in Korea. In total 20,203 subjects visited the Health Promotion Center at the Samsung Medical Center for a physical check-up in 1998. Subjects with a previous diabetes history and/or an FPG of ≥7.0 mM/L (n=1,821) were excluded. Because almost all subjects who visited the Health Promotion Center were middle-aged, we included only persons aged from 35 to 65 yr (inclusive). Finally, 15,936 subjects were included in this study. A proportion of the subjects visited the Health Promotion Center annually. About 23% of these subjects [2,964 (2,009 men, 955 women)/

15,936] revisited the Health Promotion Center voluntarily in 2003. The examination methodology used was the same on both occasions. In 2003, after a 5-yr follow-up, subjects being treated for diabetes or those with an FPG ≥7.0 mM/L were classified as having newly developed diabetes. All subjects were classified into four groups according to their baseline FPG values (Group 1: FPG <5.0, n=765; Group 2: 5.0 ≤FPG <5.6, n=1,244; Group 3: 5.6≤FPG <6.1, n=679; Group 4: 6.1≤FPG <7.0 mN/L, n=276). Height and weight were measured with subjects wearing light clothing without shoes in the morning. Blood pressure was measured with a mercury sphygmomanometer on the right arm with the subjects in a sitting position after a 5-min rest. Body mass indexes (BMI) were calculated as weight in kilograms divided by height squared in meters. This study was approved by the Internal Review Board of Samsung Medical Center.

Analytical methods

Plasma glucose was measured in duplicate using an autoanalyzer (Hitachi, Tokyo, Japan) and the hexokinase method. The interassay coefficient of variation was 1.6%. Total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were also measured using an autoanalyzer (Hitachi, Tokyo, Japan).

Statistics

Data are expressed as means±SD. Cox regression analyses were performed to determine the hazards ratios of diabetes development for each group, after controlling for age, gender, BMI, change of BMI, parental history of diabetes, systolic blood pressure, diastolic blood pressure, serum LDL-cholesterol, triglyceride, and HDL-cholesterol. To determine the optimal FPG value for the prediction of future diabetes, receiver operator characteristics curve analysis was performed. Statistical analyses were performed using SPSS/PC$^+$ (SPSS, Inc., Chicago, IL, U.S.A.). Differences were considered statistically significant at $p<0.05$.

RESULTS

The baseline characteristics of the study subjects are presented in Table 1. Because this study involved subjects who voluntarily attended Health Promotion Center for both baseline and follow-up examinations, we compared the characteristics of subjects that only received a baseline examination with those that received baseline and follow-up examinations. The total follow-up participation rate was 22.8% (28.1% in men, 13.4% in women). Follow-up participation rates in each group were 16.1% in group 1, 18.9% in group 2, 20.5% in group 3, and 20.9% in group 4. As presented in Table 1, FPG values, ages and the proportion of male subjects in baseline and follow-up groups, were significantly higher than in the baseline only group. Person-year diabetes incidence according to the baseline FPG categories were 0.1% in Group 1, 0.2% in Group 2, 0.7% in Group 3, and 5.5% in Group 4.

In a previous study of subjects who attended our Health Promotion Center, age, a male sex, a parental history of diabetes, BMI, systolic and diastolic blood pressure, serum LDL-cholesterol, triglyceride and HDL-cholesterol were found to be positively associated with the presence of diabetes (7). Therefore, we tried to investigate the relationship FPG baseline values and incidence of newly developed diabetes after controlling for these variables. By Cox regression analyses after controlling for age, gender, BMI, change of BMI, parental history of diabetes, systolic blood pressure, diastolic blood pressure, serum LDL-cholesterol, triglyceride, and HDL-cholesterol, no significant difference was found between Group 1 and Group 2 in terms of the incidence of diabetes. However, the incidence of diabetes in Group 3 was significantly

Table 1. Baseline characteristics according to baseline FPG

	Baseline only					Baseline and follow-up				
	Group 1	Group 2	Group 3	Group 4	Total	Group 1	Group 2	Group 3	Group 4	Total
No. (%)	3,976 (23.7)	5,321 (41.0)	2,630 (20.3)	1,045 (8.1)	12,972	765 (25.8)	1,244 (42.0)	679 (22.9)	276 (9.3)	2,964
FPG (mM/L)	4.68±0.23	5.24±0.16	5.76±0.16	6.39±0.24	5.27±0.54	4.69±0.23	5.24±0.16	5.76±0.16	6.40±0.22	5.32±0.54*
Age (yr)	46.8±7.9	48.3±8.0	49.7±7.9	51.4±7.8	48.4±8.0	47.7±7.3*	48.6±6.8	49.8±6.8	50.7±7.2	48.8±7.0*
Male sex (%)	42.2	54.1	68.3	76.4	44.9	51.0*	68.0*	79.4*	84.8*	67.8*
Baseline BMI (kg/m^2)	22.7±2.7	23.4±2.7	24.1±2.8	24.6±2.7	23.4±2.8	22.7±2.6	23.4±2.5	24.2±2.5	24.6±2.2	23.5±2.6
Baseline BMI ≥25 kg/m^2 (%)	19.5	26.2	35.2	42.6	27.4	18.0	24.7	37.6	40.2	27.4
Parental history of diabetes (%)	7.6	8.2	10.3	11.0	8.6	6.0	7.1	8.5	9.4	7.4†
Years of follow-up (%)						4.88±0.36	4.93±0.35	4.97±0.31	4.97±0.35	4.97±0.35
Person-year incidence of diabetes (%)						0.1	0.2	0.7	5.5	3.8

†$p<0.05$, *$p<0.01$ compared to the baseline only group by the t-test or χ^2 test. Group 1: FPG <5.0; Group 2: 5.0 ≤FPG <5.6; Group 3: 5.6≤FPG <6.1; Group 4: 6.1≤FPG <7.0 mM/L. FPG, fasting plasma glucose; BMI, body mass index.

Table 2. Hazard ratio of diabetes development according to baseline FPG by multivariate Cox regression analyses

		Model 1						Model 2					
		Total		Men		Women		Total		Men		Women	
		Exp(B) (95% CI)	*p*	Exp(B) (95% CI)	*p*	Exp(B) (95% CI)	*p*	Exp(B) (95% CI)	*p*	Exp(B) (95% CI)	*p*	Exp(B) (95% CI)	*p*
vs group1	Group 2	1.46 (0.46-4.59)	NS	1.61 (0.18-14.40)	NS	1.32 (0.34-5.19)	NS	1.48 (0.47-4.66)	NS	1.69 (0.19-15.19)	NS	1.42 (0.36-5.67)	NS
	Group 3	4.88 (1.65-14.41)	0.004	9.23 (1.22-70.02)	0.032	2.02 (0.49-8.37)	NS	4.77 (1.60-14.15)	0.005	9.50 (1.25-72.24)	0.030	1.91 (0.45-8.21)	NS
	Group 4	36.91 (13.11-103.61)	<0.001	74.83 (10.3-543.02)	<0.001	16.12 (4.43-58.63)	<0.001	34.57 (12.18-98.10)	<0.001	76.02 (10.42-544.51)	<0.001	15.46 (4.08-58.61)	<0.001

Group 1: FPG <5.0; Group 2: 5.0 ≤FPG <5.6; Group 3: 5.6 ≤FPG <6.1; Group 4: 6.1 ≤FPG <7.0 mM/L; NS, not significant. The dependent variable was the development of diabetes. Independent variables in model 1 were age, gender, BMI, change of BMI, and a parental history of diabetes, and in model 2 were systolic blood pressure, diastolic blood pressure, serum LDL-cholesterol, triglyceride, HDL-cholesterol and the variables of model 1.

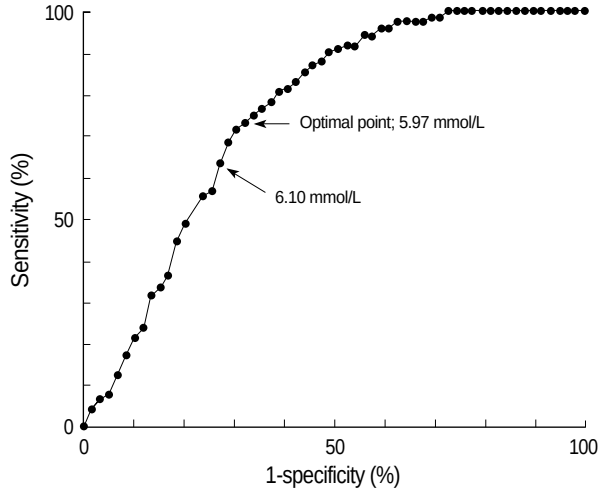

Fig. 1. Optimal value of FPG for diabetes prediction by ROC analysis. Area under the curve=0.872, p<0.001. Sensitivity and specificity at a FPG of 5.97 mM/L were 0.74 and 0.90, respectively, and those at 6.10 mM/L were 0.63 and 0.93, respectively.

higher than in Group 1 [hazards ratio 4.88 (1.65-14.41), p= 0.004] and the hazards ratio for diabetes in Group 4 was 36.91 (13.11-103.61) compared to Group 1 (p<0.001) (Table 2). In a subgroup analysis of men, the incidence of diabetes in Group 3 was found to be significantly higher than that in Group 1. However in women, no significant difference was found between Group 1 and Group 3.

Receiver operator characteristics curve analysis was performed to investigate the optimal value of FPG for predicting future diabetes (area under the curve 0.872, p<0.001) (Fig. 1), and identified a lower limit FPG limit of 5.97 mM/L as the fasting category that gave the best combination of sensitivity and specificity. In subgroup analyses, the corresponding optimal values were 5.97 mM/L for men and 5.86 mM/L for women. Overall sensitivity and specificity at an FPG of 5.97 mM/L were 0.74 and 0.90, respectively. The comparable figures at 6.10 mM/L were 0.63 and 0.93, respectively, and those at 5.6 mM/L were 0.83 and 0.75.

DISCUSSION

To the best of our knowledge, this is the first study to attempt to identify an FPG cutoff value for the prediction of future diabetes development in Korean subjects. Recently, the American Diabetes Association (ADA) expert committee on the diagnosis and classification of diabetes mellitus suggested that the cut-off for impaired fasting glucose should be reduced from 6.1 mM/L to 5.6 mM/L. They reported that the FPG value, by receiver operator characteristics curve analysis, closest to the ideals of 100% sensitivity and 100% specificity over the glycemic range of 4.5-7.0 mM/L was 5.7 mM/L in a Dutch population, 5.4 mM/L in a Pima Indian population, 5.4 mM/L in a Mauritian population, and 5.2 mM/L in a San Antonio population (8).

However, in the present study when a baseline FPG of <5.6 mM/L was investigated no difference was observed in the incidence of diabetes versus baseline by Cox regression analysis. However, subjects with an FPG ≥5.6 mM/L and <6.1 mM/L showed significantly higher diabetes incidence after a 5-yr follow-up period than those with an FPG of <5.6 mM/L. Our data suggest that the incidence of diabetes development started to increase before an FPG of 6.10 mM/L (the lower limit value originally proposed for impaired fasting glucose) in our Korean population. By subgroup analyses according to gender, we found a significant difference of diabetes incidence using an FPG cut off of 5.6 mM/L in men, but no significant difference in women. In the present study, men were older, more obese, had higher blood pressures, poorer lipid profiles, and higher FPGs than women (data not shown). We consider that the explanation for the observed difference between men and women is provided by their markedly different participation rates at follow-up (28.1% in men, 13.4% in women, p<0.001). In our study, the optimal FPG cut off value for predicting future diabetes development using receiver operator characteristics curve analysis was 5.9 mM/L, which is somewhat higher than that reported by other studies. We are unable do explain this discrepancy, though it may be due to

ethnic differences. In view of our lack of oral glucose tolerance test data, we cannot conclusively state that the optimal FPG cut off value in Korean subjects is higher than in other ethnic groups. However, it is noteworthy that in low risk populations like the Dutch and Korean populations that the optimal FPG cut-off values for separating high and low risk subjects are higher than in high risk populations like the Pima Indians, Mexican Americans, and others.

The most important limitation of the present study is the incompleteness of the diabetes diagnoses, because of a lack of oral glucose tolerance test (OGTT) data. This incompleteness is a potential source of result distortion, because it is expected that some subjects with minor FPG abnormalities at baseline developed diabetic OGTT, but not overt diabetes five years later. However, comparable reports on the prevalence of diabetes using WHO criteria or ADA criteria in the Korean population (7.1% by the WHO criteria, 7.7% by the ADA criteria after adjusting to the standard world population of Segi), reduces this concern (9). Another study in the Korean population reported that the use of FPG data without OGTT data to diagnose diabetes might fail to detect a some diabetics, especially in elderly subjects (10). In the present study, subjects older than 65 yr were excluded. Another major limitation of our study is that it was not a population-based study. The present study included only middle-aged persons, and these attended a health promotion center for an annual physical check-up. Thus they may have had more health concerns and health problems than the general population. Actually, in the present study, those who participated in the baseline and follow-up studies were older and had higher FPG values than those who submitted for the baseline study only. Therefore, our findings should be confirmed by a population-based prospective study.

In conclusion, the data obtained during the present study shows that risk of future diabetes starts to increase from below an FPG level of 6.1 mmol/L, and thus, suggests the importance of our making a concentrated effort to reduce the risk factors of diabetes early during the development of fasting glucose impairment.

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