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Should the lower limit of impaired fasting glucose be reduced from 110 mg/dL in Korea?

Seungho Ryu[a,b], Hocheol Shin[a,*], Yoosoo Chang[c], Ki Chul Sung[d], Jaechul Song[e], Soo-Jin Lee[e]

[a]*Department of Family Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul 110-746, South Korea*
[b]*Department of Occupational Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul 110-746, South Korea*
[c]*Medical Screening Center, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul 110-746, South Korea*
[d]*Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul 110-746, South Korea*
[e]*Department of Occupational and Environmental Medicine, Hanyang University College of Medicine, Seoul 133-791, South Korea*

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Abstract

The aims of this study were to determine if impaired fasting glucose should be redefined as a fasting plasma glucose (FPG) of 100 to 125 mg/dL (5.6-6.9 mmol/L) in Korea. A prospective cohort study was undertaken involving 13 189 male workers aged 30 to 59 years who did not have medication for diabetes, a history of any cancer, or a fasting glucose level of 126 mg/dL or higher at the initial examination between January 1999 to December 2000. Subjects were reexamined at periodic annual health examination over a 5-year period. The receiver operating characteristic curve for predicting the future onset of diabetes was derived by plotting the sensitivity against 1 − specificity for a baseline FPG of less than 126 mg/dL. The age- and body mass index–adjusted incidence density of type 2 diabetes mellitus was examined according to the percentile of the distribution for the baseline FPG. The baseline FPG for predicting the future onset of diabetes at a point on the receiver operating characteristic curve that was closest to the ideal 100% sensitivity and 100% specificity was 92 mg/dL. There was a threshold for the age- and body mass index–adjusted incidence density of diabetes in the group with FPG of 93 to 95 mg/dL, at a mean of 93.9 mg/dL. Lowering the lower limit of impaired fasting glucose to 100 mg/dL (5.6 mmol/L) would optimize its sensitivity and specificity for predicting the future onset of diabetes in Korea.

1. Introduction

In 1997, the American Diabetes Association (ADA) decided to lower the cutoff point for the fasting plasma glucose (FPG) level from 140 to 126 mg/dL for diabetes, and an FPG level between 110 mg/dL and 125 mg/dL was defined as impaired fasting glucose (IFG) [1]. The World Health Organization adapted this new criterion in 1999 [2]. In November 2003, the ADA proposed the new criteria for IFG as 100 to 125 mg/dL [3]. The justification for this new criteria was that the data from Pima Indians showed that the risk of diabetes increases markedly at an FPG concentration of higher than ~100 mg/dL [4].

However, there might also be ethnic differences in the criteria for IFG. For example, a different mechanism for type 2 diabetes mellitus has been suggested in Korea. Most type 2 diabetic patients in Korea are not obese, and many lose significant amounts of weight during the course of developing diabetes [5]. Moreover, insulin sensitivity in the first-degree relatives of Korean type 2 diabetic patients was not lower than that in the control subjects [6]. Therefore, an insulin deficiency rather than insulin resistance is suggested to be the major pathogenic mechanism for most Korean type 2 diabetic patients.

Although there might be an ethnic difference in the pathogenic mechanism for type 2 diabetes mellitus, little research aimed at evaluating the cutoff values for the

* Corresponding author. Kangbuk Samsung Hospital, Jongro-Gu, Seoul 110-746, South Korea. Tel.: +82 2 2001 2278; fax: +82 2 2001 2913.
E-mail address: hcfm.shin@samsung.com (H. Shin).

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Table 1
Baseline characteristics of the participants

	Total N = 13 189
Age (y)	36.6 ± 4.7
30-39	9872 (74.9)
40-49	3122 (23.7)
50-59	195 (1.5)
FPG (mg/dL)	85.4 ± 10.3
WBC count (10^3/mm^2)	6.3 ± 1.6
Uric acid (mg/dL)	5.8 ± 1.2
Total cholesterol (mg/dL)	187.3 ± 33.9
Triglyceride (mg/dL)	123.4 ± 92.8
HDL-C (mg/dL)	49.0 ± 10.5
BMI (kg/m^2)	23.1 ± 2.8
SBP (mm Hg)	122.2 ± 11.6
DBP (mm Hg)	78.3 ± 8.7
Smoking	
Nonsmoker	4808 (36.4)
Ex-smoker	2436 (18.5)
Smoker	5945 (45.1)

Values are expressed as mean ± SD or n (%). WBC indicates white blood cell.

baseline FPG for predicting the future onset of diabetes in Asian populations has been carried out.

The aims of this study were to determine if IFG should be redefined as an FPG of 100 to 125 mg/dL (5.6-6.9 mmol/L) in Korea.

2. Methods

2.1. Subjects

Our study is a prospective cohort study, designed to assess risk factors for major diseases, including hypertension, dyslipidemia, and diabetes, among Korean men who are workers at one of the biggest semiconductor manufacturing facility in Korea. All workers were required to participate in annual or biennial health examinations by the Industrial Safety and Health Law in Korea. A total of 15 079 Korean male workers aged 30 to 59 years participated in health examination at the Kangbuk Samsung Hospital, School of Medicine, Sungkyunkwan University, between January 1999 to December 2000. Among these, 133 (0.9%) were excluded: 35 (26.3%) were taking medication for diabetes; 5 (3.8%) had a history of any cancer; 93 (69.9%) have a fasting glucose level of 126 mg/dL or higher at the initial examination. The diabetes-free cohort thus comprised 14 946 men and they were reexamined at the same hospital over 5 successive years until December 2004. We also excluded 1757 men from this cohort who did not participate in consecutive annual health examinations during follow-up. Finally, 13 189 Korean male workers from a semiconductor manufacturing facility were enrolled in the analysis.

2.2. Measurements

The blood samples were collected after more than 12 hours of fasting, and the FPG, total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were measured enzymatically using an automatic analyzer (Advia 1650 Autoanalyzer, Bayer Diagnostics, Leverkusen, Germany). Seated blood pressure levels were obtained by trained nurses using standard mercury sphygmomanometers. Two readings were taken at first and fifth Korotkoff sounds to estimate systolic blood pressure (SBP) and diastolic blood pressure (DBP). The average of 2 readings was used. Height and weight were measured after an overnight fast with the subjects wearing a lightweight hospital gown and without shoes. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters.

2.3. Statistical methods

2.3.1. Receiver operating characteristic analysis

In this study, a receiver operating characteristic (ROC) curve [7] for predicting the future onset of diabetes was derived by plotting the sensitivity vs 1 − specificity for the baseline FPG of less than 126 mg/dL. The optimal cutoff point was defined as the closest point on the ROC curve to the point at a 1 − specificity of 0 and a sensitivity of 100%. The areas under the curves represent the probability that a subject chosen at random, who had diabetes or who developed diabetes, had a higher test value than a subject who did not have or did not develop diabetes.

2.3.2. Frequency distributions

The age- and BMI-adjusted incidence density of type 2 diabetes mellitus was examined according to the percentile of the distribution for the baseline FPG. Those with FPG of less than 80 mg/dL formed the lowest group, those with FPG of 110 mg/dL or higher formed the highest group, and the remainder were divided into deciles. This approach was used because it provided the highest precision for examining

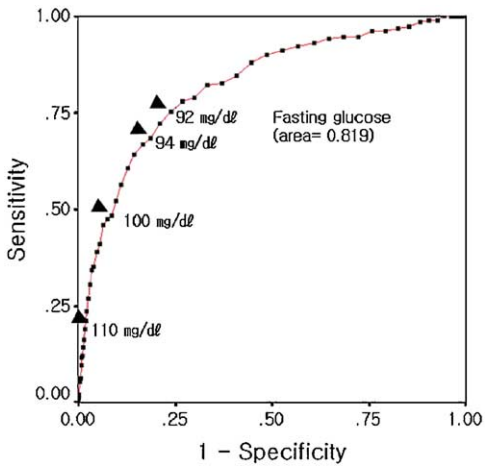

Fig. 1. Receiver operating characteristic curves for the baseline FPG for predicting the future onset of diabetes. The baseline FPG level at the point on the ROC curve that was closest to the ideal of 100% sensitivity and 100% specificity was 92 mg/dL.

Table 2
Performance of various cut points for predicting future onset of diabetes

Cut point of FPG (mg/dL)	Sensitivity (%)	Specificity (%)
90	78.8	69.5
91	77.8	72.5
92	75.1	75.5
93	72.0	78.4
94	68.3	81.0
95	66.7	83.1
96	64.0	85.1
97	60.3	86.8
98	56.1	88.7
99	51.9	90.0
100	48.1	91.0
110	20.6	98.0

the possible threshold effects, while maintaining adequate numbers within each percentile band. In this study, diabetes was defined as having an FPG level of 126 mg/dL or higher alone, and diabetes was viewed as being a chronic condition, that is, once a subject met the criteria for type 2 diabetes mellitus, the subject was considered to be a diabetic for the remainder of the follow-up period. Incidence density was expressed as the number of patients divided by the person-years from the baseline until the development of diabetes or until the final examination. The age and BMI standardization was estimated using the direct method to the age and BMI structure of the subjects.

The statistical analysis for the data was carried out using SPSS version 12.0 software (SPSS, Chicago, IL).

3. Results

Table 1 shows the baseline characteristics of the subjects (N = 13 189). Their mean age ± SD was 36.6 ± 4.7 years. The number of incident cases for diabetes (FPG ≥ 126 mg/dL) during the 53 969 person-year follow-up was 190.

At the baseline, the mean (±SD) FPG, total cholesterol, triglyceride, and HDL-C levels were 85.4 (±10.3), 187.3 (±33.9), 123.4 (±92.8), and 49.0 (±10.5) mg/dL, respectively. The mean BMI was 23.1 (±2.8) kg/m^2; the mean (±SD) SBP and DBP were 122.2 (±11.6) and 78.3 (±8.7) mm Hg, respectively (Table 1).

Fig. 1 shows the analyses for the characteristics of the ROC for the incidence of diabetes. The cutoff point that maximizes the sum of the sensitivity and specificity can be used to discriminate between the groups of subjects who have a high risk of contracting diabetes. The baseline FPG level at the point on the ROC curve that was closest to the ideal of 100% sensitivity and 100% specificity was 92 mg/dL. The sensitivity and specificity of 92 mg/dL were 75.1% and 75.5%, respectively. At the lower limit for the baseline IFG (110-125 mg/dL), as currently defined, the sensitivity and specificity for the future onset of diabetes were 20.6 and 98.0%, respectively (Table 2, Fig. 1).

The age- and BMI-adjusted incidence density of type 2 diabetes mellitus was examined according to the percentile of the distribution of the baseline FPG (Fig. 2). The mean number of participants per percentile band was 1099 (range, 302-4038). The figure provides evidence of a threshold in the group with baseline FPG of 93 to 95 mg/dL. Below this, the incidence of diabetes was either lower or rare, and above this, the incidence was considerably higher. In the group with FPG of 93 to 95 mg/dL, the age- and BMI-adjusted incidence density of type 2 diabetes mellitus was 3.92 per 1000 person-years, and the mean baseline FPG value was 93.9 ± 0.8 mg/dL. In the group with FPG of 96 to 99 mg/dL, the age- and BMI-adjusted incidence density of type 2 diabetes mellitus was 9.01 per 1000 person-years, and the mean baseline FPG value was 97.3 ± 1.1 mg/dL. The incidence density of type 2 diabetes mellitus was highest in the group with FPG of 110 to 125 mg/dL. In this group, the age- and BMI-adjusted incidence density of type 2 diabetes mellitus was 31.1 per 1000 person-years.

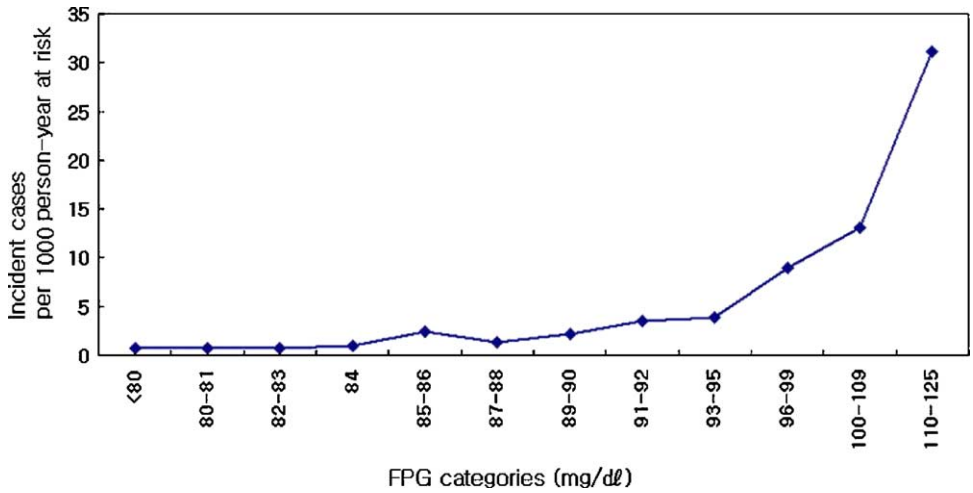

Fig. 2. Age- and BMI-adjusted incidence density of diabetes according to baseline FPG categories. The incidence density of diabetes is defined by FPG alone in subjects with a baseline FPG of less than 126 mg/dL.

4. Discussion

The category IFG refers to a metabolic stage that is intermediate between the upper limit of the normal FPG and the lower limit of diabetic FPG, which is similar to an impaired glucose tolerance (IGT) between the upper limit of a normal 2-hour postprandial plasma glucose (2-hour PG) and a lower limit of diabetic 2-hour PG. In November 2003, the ADA proposed new criteria for IFG as being 100 to 125 mg/dL [3]. The current categories of the FPG in Korea are as follows: FPG of less than 110 mg/dL = normal fasting glucose; FPG of 110 mg/dL or higher (6.1 mmol/L) and less than 126 mg/dL (7.0 mmol/L) = IFG; FPG of 126 mg/dL or higher (7.0 mmol/L) = provisional diagnosis of diabetes.

This study examined whether IFG in Korea should be redefined as an FPG between 100 and 125 mg/dL (5.6-6.9 mmol/L). The current investigation shows that the cut point for the baseline FPG was 92 mg/dL. In this study, the overall population was fairly young and not obese. Therefore, the age- and BMI-adjusted incidence density of type 2 diabetes mellitus was examined according to the percentile of the distribution of the baseline FPG. A threshold was evident for the age- and BMI-adjusted incidence density of diabetes in the group with FPG of 93 to 95 mg/dL, at a mean of 93.9 mg/dL. These values suggest that 110 mg/dL, as a lower limit for IFG, was inappropriately high in Korea. However, it does not mean that the optimal level is FPG of 92 or 93.9 mg/dL. In reality, optimization requires consideration of the costs of predicting or not predicting a diagnosis of diabetes when diabetes does or does not ultimately develop. The costs involve economic costs of testing, diagnosis, and treatment, as well as health and social costs of failing to predict a diagnosis or predicting diabetes in someone who will not develop it. But our results show that the lowering of the lower limit of IFG from 110 to 100 mg/dL is in the right direction in our data, although it actually does not go far enough. Therefore, for purposes of consistency with international standards, the lowering the IFG cut point to 100 mg/dL (5.6 mmol/L) should be adopted in Korea.

The results of this study are similar to those reported in earlier western studies. The FPG value at the point on the ROC curves closest to the ideal 100% sensitivity and 100% specificity was 5.5 mmol/L in a Mauritius population [8]. The San Antonio Heart Study reported that lowering the fasting glucose cutoff to 5.4 mmol/L (94 mg/dL) improved the ability to predict diabetes by metabolic syndrome [9]. To our knowledge, little research has been done on Asian population to evaluate the cutoff values for the baseline FPG to predict the future onset of diabetes. Therefore, these results cannot be compared with those from other studies in Asia.

The Paris Prospective Study reported that the risk of developing diabetes over 3 years was greater among middle-aged men with an FPG of higher than 110 mg/dL (6.1 mmol/L) than it was for those with a lower FPG [10]. In addition, several studies showed evidence that high, but not diabetic, FPG values were associated with cardiovascular disease and the future onset of diabetes [11-13]. However, in these studies, it is also not possible to determine if 110 mg/dL (6.1 mmol/L) is the ideal lower limit for IFG.

In this study, because the 2-hour PG was not measured, the cut point for the baseline FPG for predicting the future onset of diabetes as defined by an oral glucose tolerance test (OGTT) could not be determined, neither could the predictive powers of the IFG and IGT for the development of diabetes be compared. A western study showed that IGT is more prevalent than IFG in most populations, and it is more sensitive (but slightly less specific) for identifying people who will later develop diabetes [14]. A study in Korea also reported similar results: the prevalence of IGT was also higher than that of IFG by the 1997 ADA criteria (23.5% vs 10.0% men, 23.7% vs 7.5% women), and the 1997 ADA fasting criteria were less sensitive for diagnosing diabetes than the OGTT-based World Health Organization criteria [15]. Therefore, reducing the lower limit of IFG to 100 mg/dL by the ADA recommendation will also increase the sensitivity and make the group identified more similar to IGT with respect to the risk of contracting diabetes in Korea.

This study has some limitations. First, our study population only involved men and, consequently, whether the same ROC cut points apply to women is unknown. So, our finding needs to be tested in other populations including women. Second, the diagnosis of diabetes was made based only on the FPG level. This approach will lead to slightly lower estimates of the incidence than would be obtained from the combined use of the FPG and OGTT. However, the ADA recommended that for epidemiological studies, estimates of the prevalence and incidence of diabetes should be based on an FPG of 126 mg/dL or higher (7.0 mmol/L) [16]. Third, the subjects in this study were younger than in the other study; 98.6% of them were in their thirties and forties. One cohort study in Korea reported that the incidence of diabetes among middle-aged Korean men was 5.01 per 1000 person-years, in which 13 983 middle-aged men in Seoul, Korea, had been followed up for 3 years from 1993, and the criterion for diabetes was having fasting glucose level of 140 mg/dL or higher [17]. In this study, age standardization incidence density was 4.7 per 1000 person-years. Although these 2 results cannot be compared directly because the diagnostic criteria used were different (140 vs 126), the result in the present study was much lower. So, this study may lead to slightly lower estimates of cutoffs for the baseline FPG to predict the future diabetes.

With all these limitations, this study is the first to determine the baseline FPG cutoff values for predicting the future onset of diabetes in Asia. Therefore, ethnic differences can be compared using these data because almost all previous data only included western populations.

In conclusion, these results show that the cut point for the baseline FPG was 92 mg/dL and that a threshold was evident for the age- and BMI-adjusted incidence of diabetes in the group with FPG of 93 to 95 mg/dL, at a mean of

93.9 mg/dL. So, lowering the IFG cutoff point to 100 mg/dL (5.6 mmol/L) should be adopted to optimize its sensitivity and specificity for predicting the future onset of diabetes in Korea.

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