Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Glycaemic and haemoglobin A1c thresholds for detecting diabetic retinopathy: The fifth Korea National Health and Nutrition Examination Survey (2011)

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ARTICLE INFO

Article history:
Received 13 August 2013
Received in revised form
25 February 2014
Accepted 2 April 2014
Available online 13 April 2014

Keywords:
Diabetic retinopathy (DR)
Diagnosis
Haemoglobin A1c (HbA1c)
Fasting plasma glucose (FPG)

ABSTRACT

Aims: Few representative population-based data are available regarding glycaemic and HbA1c thresholds for detecting diabetic retinopathy (DR) in Asia. We investigated the association between DR and fasting plasma glucose (FPG) and HbA1c levels among Korean adults.

Methods: Using data from the Korea National Health and Nutrition Examination Survey (2011), a total of 5212 adults (≥19 years old) were analysed. When participants had diabetes mellitus and/or a suspicion of DR in two-field nonmydriatic fundus photography, seven standard photographs were obtained after pupil dilatation (75.9% of men, 75.0% of women among the subjects). DR was defined as the presence of ≥1 retinal microaneurysms or blot haemorrhages with or without more severe lesions. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-off value for HbA1c or FPG.

Results: The overall glycaemic thresholds for DR were 6.3 mmol/l for FPG and 6.2% (44 mmol/mol) for HbA1c. The optimal thresholds did not differ by age group. The sensitivities and specificities were 82.6% and 91.2% for FPG and 93.9% and 89.7% for HbA1c, respectively. The diagnostic discrimination was better for HbA1c than FPG for DR—area under curve: 0.908 for FPG and 0.953 for HbA1c ($p = 0.007$). After being controlled for other covariates, the odds ratio

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Abbreviations: KNHANES, Korea National Health and Nutrition Examination Survey; DR, diabetic retinopathy; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c.

http://dx.doi.org/10.1016/j.diabres.2014.04.003

for the risk of DR increased significantly in a consistent way from 6.2% (44 mmol/mol) for HbA1c and 6.3 mmol/l for FPG.

Conclusions: According to these nationally representative data, the current diabetes diagnostic values for FPG and HbA1c based on DR may be lower for the Korean population.

1. Introduction

The prevalence of diabetes has steadily and dramatically increased throughout the world, including Korea. According to the Korean Diabetes Association (KDA), approximately 3.2 million Korean people aged at least 30 years (10.1%) had diabetes in 2010, and diabetes will affect 6.0 million people in Korea by 2050; this prevalence is estimated to be twice that of 2010 [1]. The dramatic increase in the diabetic population will inevitably be accompanied by increased diabetic complications and enormous health costs. Therefore, early detection and screening of high-risk individuals for diabetes with appropriate intervention should be emphasised in clinical practice.

The diagnostic criteria and cut-off values for fasting plasma glucose (FPG) and haemoglobin A1c (HbA1c) levels for diabetes have been continuously updated and modified during the past several decades. Before the late 1990s, diagnosing diabetes was based on clinical symptoms and the mean glucose value plus two standard deviations of blood glucose levels [2]. Since 1999, diagnostic criteria were defined using large epidemiologic studies assessing bimodal distributions and thresholds for microvascular complications [3,4].

Diabetic retinopathy (DR) is a specific and early clinical complication related to diabetes and has served as the basis for determining diagnostic cut-off points for diabetes mellitus [5,6]. Currently, some large epidemiologic studies are available about the relationship between the prevalence of retinopathy and glycaemic measures, including FPG, 2-h plasma glucose (2hPG), and HbA1c. The datasets from Pima Indians, an Egyptian study, the Third National Health and Nutritional Examination Survey (NHANES), and the DETECT-2 collaboration Group showed the cut-off levels for diagnosing diabetes that were based on the association with DR [6–9]. Based on these results, many recently published clinical recommendations specify diagnostic criteria for diabetes as an FPG of 7.0 mmol/l and an HbA1c of 6.5% (48 mmol/mol) [10–12]. However, some studies show somewhat different optimal cut-off values based on the presence of DR, the subject population, ethnicity, age range of inclusion, or analytical methods [13–16]. Moreover, few published data have demonstrated the association of FPG or HbA1c with retinopathy prevalence using a nationwide survey, particularly in Asian populations.

The aims of this study were to investigate the association between levels of FPG and HbA1c with diabetic retinopathy and to determine the optimal cut-offs of FPG and HbA1c for detecting diabetic retinopathy in a representative Korean population.

2. Subjects and methods

2.1. Study population

This study used data from the 5th KNHANES, which was conducted by the Korean Ministry of Health and Welfare in 2011. This survey was a nationally representative study of non-institutionalised civilians using a stratified, multistage probability sampling design. Sampling units were defined based on the data regarding household registries, including geographic area, sex, and age groups. The KNHANES was composed of a health interview survey, a health examination survey, and a nutrition survey conducted by trained investigators. Additional details about the study design and methods are provided elsewhere [17,18]. A total of 8055 of 10,589 subjects (76.1%) participated in the health interview survey and the health examination survey. Fundus photographs were available for 7654 subjects (72.3%). Participants aged 19 years and over, including those with known diabetes and with gradable retinal photographs and at least one measure of glycemia (FPG and HbA1c), were included [18]. Pregnant women and subjects missing FPG, HbA1c or fundus photography were excluded. All of the participants provided written informed consent to participate in the study. This study was approved by the Institutional Review Board of the Catholic University of Korea. The investigations were performed in accordance with the principles of the Declaration of Helsinki as revised in 2000.

2.2. Definition of diabetes

Diabetes was diagnosed on the basis of an FPG of $\geq$7.0 mmol/l, HbA1c $\geq$ 6.5% (53 mmol/mol), self-reported diagnosed diabetes, or current use of oral hypoglycaemic agents and/or insulin according to the clinical practice guidelines from the KDA [12].

2.3. Diagnosis of diabetic retinopathy (DR)

After 5 min of dark adaptation, retinal photographs were taken using a digital nonmydriatic fundus camera (TRC-NW6S, TOPCON, Japan) with a Nikon D-80 digital camera (Nikon, Tokyo, Japan), and digital fundus images were obtained from all participants aged 19 years and older. For each participants, one 45° nonmydriatic digital retinal image centred on the fovea was taken per eye (2 images per person in total) [19,20].

In participants who had a history of diabetes mellitus or a random blood glucose level of $\geq$11 mmol/l and/or suspicion of DR in nonmydriatic fundus photography, seven standard photographs from the Early Treatment for Diabetic Retinopathy

Study (ETDRS) were obtained from each eye after pharmacological pupil dilatation. Among the subjects, photographs were taken in 75.9% of men ($n = 278$) and 75.0% of women ($n = 266$) [19,20]. A retinopathy severity score was assigned according to the ETDRS severity scale. DR was defined as the presence of one or more retinal microaneurysms or blot haemorrhages with or without more severe lesions (hard exudates, soft exudates, intraretinal microvascular abnormalities, venous bleeding, new retinal vessels, and fibroproliferations) [19,20]. The final retinopathy grading for each participant was based on the diagnosis in the more severely affected eye. Two ophthalmologists reviewed all the files. The intergrader and intragrader agreements were $\kappa > 0.80$. The primary outcome was any diabetic retinopathy.

2.4. Measurements

By specially trained examiners, the blood pressure of subjects, who were seated for at least 5 min, was measured using a mercury sphygmomanometer (Baumanometer; Baum, Copiague, NY). The mean value of three separate blood pressure readings was used. Hypertension was defined as a systolic blood pressure (SBP) $\geq$ 140 mmHg, a diastolic blood pressure (DBP) $\geq$90 mmHg, or self-reported current use of antihypertensive medications [21]. Waist circumference (WC) was measured to the nearest 0.1 cm in a horizontal plane at the midpoint between the iliac crest and the costal margin at the end of a normal expiration. The body mass index (BMI) was calculated as the individual's weight in kilograms divided by the square of the individual's height in meters.

The blood samples were obtained after a minimum fasting time of 8 h. HbA1c values were measured using high-performance liquid chromatography (HLC-723G7, Tosoh, Japan). Regarding the HbA1c, periodic checking and comparisons of the test results with the reference materials from reference institutes such as ''National Glycohemoglobin Standardization Program (NGSP)'' were performed three times during the 2011 KNHANES survey and the results were acceptable. The serum levels of fasting glucose, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triglycerides, and creatinine were measured enzymatically in a central laboratory using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). The detailed methods for comparing and verifying the validity and reliability in each survey are described elsewhere [18,22]. Lifestyle-related or other characteristics, including diabetic duration, diabetes treatment, and subjects' co-morbidities were ascertained using a structured questionnaire.

2.5. Statistical analysis

The data were analysed using the appropriate sample weights provided by the Korea Centers for Disease Control and Prevention. All data were presented as the mean $\pm$ standard error (SE) for continuous variables and as a frequency percentage (SE) for categorical variables. Statistical analyses were performed using the SAS (Version 9.2; SAS Institute, Cary, NC) survey procedure to account for the complex sampling design and to provide a nationally representative prevalence estimate. Age-adjustment was also used to compare other characteristics between the subjects with DR and without DR.

Receiver operating characteristic (ROC) curve analysis was applied to determine the optimal cut-off value of FPG and HbA1c for identifying DR. Youden's index was also used to evaluate the discriminative power of FPG and HbA1c for predicting DR with the following formula: (sensitivity + specificity) $-$ 1. The associations of FPG and HbA1c were analysed using multiple logistic regression analysis after adjusting for age, sex, smoking, waist circumference, and hypertension. Sensitivity analyses were performed using the samples after excluding the individuals who were receiving anti-hyperglycaemic treatment. A p value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Clinical characteristics of the participants

After exclusion of the non-eligible subjects, 5212 patients (2213 men and 2999 women) participated in the analysis. The mean age of the subjects was 44.3 $\pm$ 0.4 years, and 49.4% were male (Table 1). The prevalence of diabetes was 10%, and the mean duration of diabetes for individuals with diagnosed diabetes was 8.0 years.

The subjects with DR were significantly older and higher FPG, HbA1c, SBP, WC, creatinine, and lipid profile levels compared with subjects without DR. Men, ever-smokers, and hypertensive subjects had a higher prevalence of DR. In addition, among the subjects with diabetes, those with DR had a longer duration of diabetes and were more likely to use insulin or oral medication than those without DR.

3.2. Prevalence of diabetic retinopathy (DR)

The overall prevalence of DR was 1.6% (95% confidence interval (CI): 1.2–2.0%). The prevalence of DR increased with age (p for trend < 0.0001). No DR was found in subjects <30 years old (Supplementary Fig. 1), regardless of the FPG level range. When confined to patients with diabetes, the prevalence of DR was 18.6% (95% CI: 14.1–23.2%), including 24.1% (18.5–29.8) in those with known diabetes, 19.1% (14.5–23.7%) in subjects with HbA1c $\geq$ 6.5% (48 mmol/mol), and 0.02% (0.0–0.1) in subjects with normal FPG and normal HbA1c.

Fig. 1 shows the prevalence of DR by deciles of the distribution of the FPG and HbA1c levels. The prevalence of DR showed a curvilinear relationship. The prevalence increased significantly between the ninth and the tenth deciles of each variable, corresponding to an FPG of 6.4 mmol/l and HbA1c of 6.4% (46 mmol/mol). The prevalence of DR for FPG and HbA1c in the tenth deciles was 16.6% with both measures, while those in the ninth deciles were 0.6% for FPG and 1.6% for HbA1c.

3.3. Optimal glycaemic thresholds for detecting diabetic retinopathy (DR)

The overall appropriate glycaemic thresholds for identifying DR by maximising the sensitivity and specificity were

Table 1 – Clinical characteristics of population according to the presence of diabetic retinopathy.

	Total	No retinopathy	Retinopathy	*p* Value	Age-adjusted *p* value
N	5212	5097	115		
Age (years)	44.3 ± 0.4	44.1 ± 0.4	61.4 ± 1.2	<0.0001	
Men (%)	49.4 (0.7)	49.3 (0.7)	58.5 (6.1)	0.150	0.034
BMI (kg/m^2)	23.7 ± 0.1	23.7 ± 0.1	24.2 ± 0.3	0.084	0.665
Waist circumference (cm)	81.2 ± 0.2	81.1 ± 0.2	86.8 ± 0.9	<0.0001	0.005
Income (lowest quartile)	14 (0.8)	13.7 (0.8)	32.4 (5.3)	<0.0001	0.965
current smoker (%)	24.1 (0.9)	24.1 (0.9)	27.3 (5.0)	0.510	0.035
Ever-smoker (%)	31.4 (1.0)	31.2 (1.0)	42.4 (6.3)	0.068	0.002
SBP (mmHg)	116.7 ± 0.4	116.5 ± 0.4	132.3 ± 2.4	<0.0001	0.001
DBP (mmHg)	76.1 ± 0.2	76.0 ± 0.2	76.5 ± 1.4	0.764	0.507
Hypertension (%)	24.3 (0.8)	23.7 (0.8)	63.6 (5.2)	<0.0001	0.0004
Diabetes	9.9 (0.5)	0.02 (0.0)	15.7 (2.0)	<0.0001	<0.0001
Diabetic duration (years)	8.0 ± 0.4	6.8 ± 0.4	11.8 ± 0.8	<0.0001	<0.0001
Diabetes treatment					
Insulin treatment (%)	0.7 (0.1)	0.5 (0.1)	14.4 (4.5)	<0.0001	<0.0001
Oral medication (%)	5.2 (0.4)	3.9 (0.3)	87.8 (3.9)	<0.0001	<0.0001
Insulin or oral med (%)	5.4 (0.4)	4.0 (0.4)	92.4 (2.9)	<0.0001	<0.0001
FPG (mmol/l)	5.3 ± 0.0	5.3 ± 0.0	8.6 ± 0.2	<0.0001	<0.0001
HbA1c (mmol/mol)	49.0 ± 0.1	48.0 ± 0.1	73.0 ± 1.5	<0.0001	<0.0001
HbA1c (%)	5.7 ± 0.0	5.6 ± 0.0	8.0 ± 0.2	<0.0001	<0.0001
Total cholesterol (mmol/l)	4.9 ± 0.0	4.9 ± 0.0	4.8 ± 0.1	0.372	0.010
Triglyceride (mmol/l)	1.5 ± 0.0	1.5 ± 0.0	2.0 ± 0.2	0.0003	0.066
Creatinine (mmol/l)	0.08 ± 0.0	0.07 ± 0.0	0.08 ± 0.0	0.004	0.007

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

6.3 mmol/l in FPG and 6.2% (44 mmol/mol) in HbA1c. The sensitivity and specificity were 82.6% and 91.2% in FPG and 93.9% and 89.7% in HbA1c, respectively (Fig. 2). The optimal thresholds did not differ by age group in the sensitivity analyses (6.3 mmol/l in FPG and 6.2% (44 mmol/mol) in HbA1c for the population ≥30 years old; 6.3 mmol/l in FPG and 6.5% (48 mmol/mol) in HbA1c for the subjects ≥40 years old, Supplementary Table 1).

Table 2 presents the prevalence of DR below and above the various cut-off points of FPG and HbA1c as well as the sensitivity, specificity, and positive and negative predictive values. Below our threshold values of 6.3 mmol/l for FPG and 6.2% (44 mmol/mol) for HbA1c, the prevalence of DR was 0.19% (0.08–0.31) for the threshold of FPG, 0.10% (0.01–0.18) for the threshold of HbA1c, and 0.07% (0.01–0.14) for the threshold of both FPG and HbA1c. The pre-existing thresholds of 7.0 mmol/l in FPG and 6.5% (48 mmol/mol) in HbA1c for diagnosing diabetes showed 73.9% and 89.6% sensitivity, respectively. In addition, when we used the pre-existing thresholds, the specificity and the positive predictive value were improved, but the sensitivity and the negative predictive value were reduced compared with the optimal glycaemic thresholds suggested from this study.

Table 3 shows the association of FPG and HbA1c with DR. After controlling for age, sex, smoking, waist circumference, and hypertension, the association was statistically significant

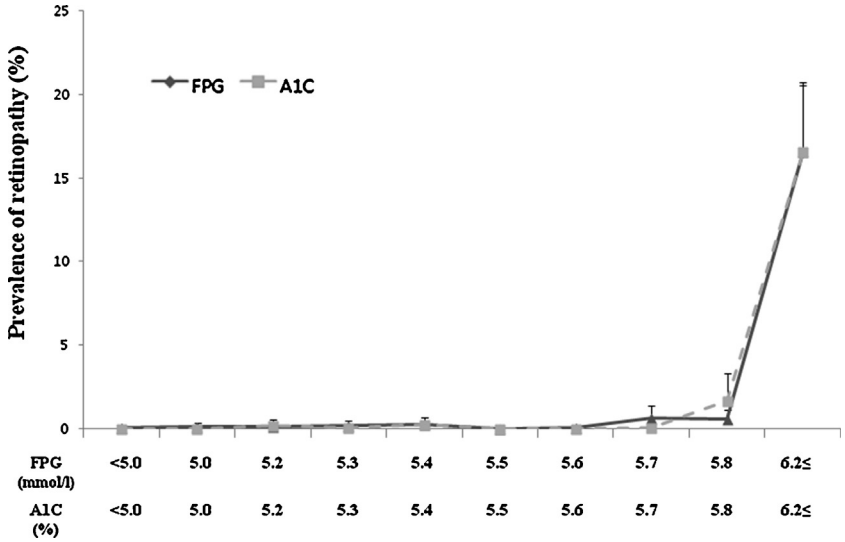

Fig. 1 – The prevalence of diabetic retinopathy by deciles of the distribution of FPG and HbA1c levels.

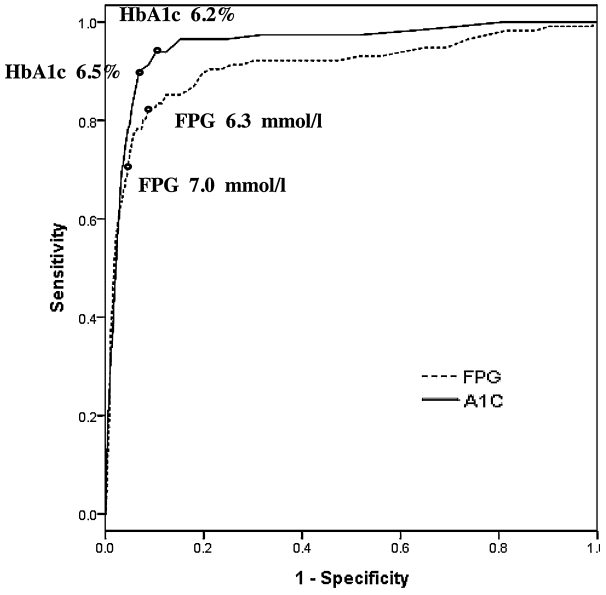

Fig. 2 – Thresholds of FPG and HbA1c for diabetes-specific retinopathy from receiver-operating characteristic (ROC) curve analyses.

in the category of 6.3–6.5 mmol/l for FPG and 6.2–6.4% (44–47 mmol/mol) for HbA1c when the criteria of <6.3 mmol/l of FPG and <6.2% (44 mmol/mol) for HbA1c were used as a reference. Furthermore, with increasing categories of FPG and HbA1c, the odds ratios increased markedly for both FPG and HbA1c. In addition, when the criteria of HbA1c < 5.7% (39 mmol/mol) and FPG < 5.5 mmol/l were used as the references, significant associations were found in the range of 6.2 to 6.6% (44–49 mmol/mol) for HbA1c and 5.5–6.2 mmol/l for FPG. With increasing values for HbA1c, the odds ratios were sharply increased. An abrupt increase in the odds ratio was observed in the range of 6.3 to 7.0 mmol/l for the FPG (Supplemental Table 1).

The area under the ROC curve for HbA1c was 0.953 (95% CI: 0.947–0.959) and was significantly larger than that of FPG (0.908 (95% CI: 0.900–0.915); p for difference = 0.007) (Fig. 2). When we excluded individuals who were receiving anti-hyperglycaemic treatment, the thresholds of detecting DR were 6.8 mmol/l in FPG and 6.0% (42 mmol/mol) in HbA1c. In this case, the AUC for HbA1c was 0.911 (95% CI: 0.903–0.919), and it was not significantly different from that for FPG (0.893; 95% CI: 0.884–0.902; p for difference = 0.755). In the subgroup analysis, the optimal cut-off values for FPG and HbA1c ranged from 6.8 to 6.9 mmol/l and 6.4% (46 mmol/mol) to 6.5% (48 mmol/mol), respectively, in women, elderly subjects ≥65 years old, obese participants with a body mass index ≥ 25 kg/m^2, and hypertensive subjects (Supplementary Table 2).

Table 2 – Percentage of cases, sensitivity, specificity, positive and negative predictive values at different cutoffs of FPG and HbA1c for detecting diabetic retinopathy.

Cutoff	Below the cutoff	Above the cutoff	Sensitivity	Specificity	Youden's index	PPV	NPV
FPG (mmol/l)							
>5.5	0.1(0)	6.4(0.8)	91.3	74.5	0.658	7.5	99.7
>6.0	0.2(0.1)	12.1(1.5)	85.2	87.6	0.728	13.4	99.6
>6.1	0.2(0.1)	12.8(1.6)	83.5	88.5	0.72	14.1	99.6
>6.2	0.2(0.1)	14.3(1.8)	82.6	89.9	0.725	15.6	99.6
>6.3	**0.2(0.1)**	**15.4(1.9)**	**82.6**	**90.8**	**0.734**	**16.8**	**99.6**
>6.4	0.2(0.1)	16.6(2.1)	80.9	91.6	0.725	17.9	99.5
>6.5	0.2(0.1)	17.5(2.3)	80	92.3	0.723	19	99.5
>6.6	0.3(0.1)	17.4(2.2)	78.3	92.7	0.710	19.4	99.5
>6.7	0.3(0.1)	19(2.4)	78.3	93.6	0.719	21.5	99.5
>6.8	0.3(0.1)	20.2(2.5)	77.4	94.2	0.716	23.1	99.5
>6.9	0.4(0.1)	21(2.7)	75.7	94.6	0.703	24	99.4
>7.0	0.4(0.1)	21.3(2.8)	73.9	95	0.689	24.9	99.4
>7.5	0.6(0.1)	24(3)	65.2	96.4	0.616	29.1	99.2
HbA1c (%)							
>5.5	0.1(0.1)	3.4(0.4)	97.4	48.4	0.458	4.1	99.9
>6.0	0.1(0)	11.5(1.4)	96.5	84.7	0.812	12.5	99.9
>6.1	0.1(0)	13.3(1.6)	93.9	87.6	0.815	14.6	99.8
>6.2	**0.1(0)**	**15.5(1.9)**	**93.9**	**89.7**	**0.836**	**17.1**	**99.8**
>6.3	0.2(0.1)	16.6(2)	91.3	91.2	0.825	19	99.8
>6.4	0.2(0.1)	19.1(2.3)	90.4	92.5	0.829	21.4	99.8
>6.5	0.3(0.1)	19.7(2.2)	89.6	93.2	0.828	22.9	99.7
>6.6	0.3(0.1)	21.2(2.4)	86.1	93.9	0.8	24.3	99.7
>6.7	0.3(0.1)	22.7(2.6)	82.6	94.6	0.772	25.7	99.6
> 6.8	0.4(0.1)	23.2(2.8)	79.1	95.1	0.742	26.5	99.5
>6.9	0.4(0.1)	24.3(3)	78.3	95.4	0.737	27.8	99.5
>7.0	0.5(0.1)	26.3(3.3)	74.8	96	0.708	29.5	99.4
>7.5	0.8(0.2)	27.9(3.7)	58.3	97.4	0.557	33.5	99

FPG, fasting plasma glucose; PPV, positive predictive value; NPV, negative predictive value.

Table 3 – Odds ratios (ORs) of diabetic retinopathy according to the categories of HbA1c and FPG.

HbA1c			FPG		
Categories (%)	Crude OR (95% CI)	Adjusted OR[a](95% CI)	Categories (mmol/l)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
<6.2	1	1	<6.3	1	1
6.2–6.4	16.84 (3.21, 88.25)	24.78 (4.81, 127.67)	6.3–6.5	20.53 (4.72, 89.32)	32.30 (7.78, 134.14)
6.5–6.7	60.00 (13.54, 265.90)	84.46 (22.40, 318.49)	6.6–6.9	25.34 (7.34, 87.45)	39.35 (11.84, 130.77)
6.8–7.0	76.53 (18.92, 309.53)	119.58 (34.66, 412.55)	7.0–7.3	55.11 (18.08,168.01)	85.89 (29.73, 248.16)
7.1≤	249.32 (84.99, 731.42)	357.45 (140.98, 906.27)	7.4≤	104.44 (49.49, 220.42)	155.46 (80.31, 300.91)

[a] Adjusted by age, sex, smoking status, waist circumference, and hypertension.

4. Discussion

In this nationwide study conducted using data from the 2011 KNHANES, we examined the associations of FPG and HbA1c with DR in a Korean population aged ≥19 years. To the best of our knowledge, this is the first population-based nationwide study in Asia. We found that the prevalence of DR sharply increased between the 9th and 10th deciles for both FPG and HbA1c. In our population, the optimal glycaemic and HbA1c cut-off levels for detecting DR were 6.3 mmol/l for FPG and 6.2% (44 mmol/mol) for HbA1c; these values were defined by the ROC curves that maximised the sensitivity and specificity for detecting diabetic retinopathy. The cut-off values between the 9th and 10th deciles for FPG and HbA1c (FPG of 6.4 mmol/l and HbA1c of 6.4% (46 mmol/mol)) were similar to those based on the ROC curve. Our cut-off points for HbA1c and FPG were lower than those of the currently used diagnostic criteria for diabetes.

Optimal cut-off thresholds for FPG and HbA1c for defining DR vary across populations. Based on ROC curve analysis, the optimal FPG threshold levels were demonstrated to be 6.8 mmol/l in the Pima Indian population [7], 6.7 mmol/l in the US population (NHANES III) [9], and 7.1 mmol/l in the AusDiab study [4]. According to the DETECT-2 Collaboration Writing Group, which included approximately 45,000 participants, the glycaemic thresholds for diabetes-specific retinopathy (defined as moderate or more severe DR) were 6.6 mmol/l for FPG, 13.0 mmol/l for 2 h PG, and 6.4% (47 mmol/mol) for HbA1c [8].

When confined to Asian populations, including Japanese and Chinese populations, the optimal cut-off values of FPG for retinopathy ranged from 5.6 to 7.2 mmol/l in the sensitivity and specificity analysis for DR [14,16,23]. We suggest that the FPG thresholds for diagnosing diabetes based on the prevalence of retinopathy, including our value of 6.3 mmol/l, are somewhat lower in Asian populations than in western populations [16,23].

In addition to FPG, HbA1c cut-off values also vary across populations. In Pima Indians, the optimal HbA1c cut-off point of 7.0% (53 mmol/mol) had 78.1% sensitivity and 84.7% specificity for detecting any retinopathy [7]. In the Hisayama study, the optimal HbA1c cut-off point of 5.7% (39 mmol/mol) was reported to have a sensitivity of 86.5% with a specificity of 90.1% [16]. Our HbA1c cut-off value was similar to those of other populations, such as the Egyptian study (6.3%; 45 mmol/mol) and NHANES III (6.0%; 42 mmol/mol) [7,24], but higher than those of a previous Japanese study (5.3–5.7%; 34–39 mmol/mol), the AusDiab study (6.1%; 43 mmol/mol), and NHANES 2005–2006 (5.5%) [4,13,16].

According to the Diabetes Prevention Program [25] and NHANES [13], 8% of people with an FPG below diabetic levels have retinopathy. The prevalence of retinopathy in subjects whose FPG value was lower than normal range was very low in the present study in contrast to previous reports from western countries. Only 0.1% of the population with a normal FPG level (less than 7.0 mmol/l) had retinopathy.

The KDA indicated that FPG and HbA1c tests are equally reliable methods for detecting individuals with diabetes or a high risk of diabetes [12]. Various reasons, such as the independence from fasting, lower biologic variability, lower pre-analytical instability, and lower day-to-day variation compared with FPG, indicate that HbA1c would be a more convenient and reliable method for diagnosing diabetes [26]. Previous studies, including the Pima Indian study and the Japanese study, tried to demonstrate the usefulness of HbA1c as diagnostic criteria of diabetes [7,16,26]. Our analysis showed the superiority of HbA1c to FPG with a larger area under the ROC curve. This finding suggests the possibility of better discrimination for DR by HbA1c than by the FPG value. Therefore, HbA1c would be a more useful glycaemic measure than FPG for a diagnostic criterion based on DR.

Differences in the prevalence of DR between ethnic groups have been reported [15,27]. The Diabetic Retinopathy In Various Ethnic groups in UK (DRIVE UK) study showed that the prevalence of any retinopathy in type 2 diabetes was highest in people of African/Afro-Caribbean descent compared with South Asians or white Europeans [15]. More data are needed to address the ethnic differences in the prevalence of diabetic retinopathy between Asian and Caucasian populations because these differences would influence the determination of a diagnostic cut-off value for HbA1c or FPG based on the presence of diabetic retinopathy. However, a lack of ethnic differences in the association of HbA1c with prevalent retinopathy in U.S. adults aged 40 years and older has also been reported [28]. According to their results, the current guideline for the diagnosis of diabetes based on HbA1c and glycaemic cut-off values could be applied equally to whites, blacks, and Hispanics.

The main strengths of this study include the following: the large population-based nationwide homogenous sample, our precise estimation of any DR from 19 years and older, and measurement of HbA1c according to internationally accepted standards using standard national quality-assurance protocols.

Several limitations of this study should be acknowledged. First, the survey was based on cross-sectional data and included all patients with diabetes regardless of the subtype of their diabetes. Second, 2-h PG values were not included in this analysis. Practically, an oral glucose tolerance test (OGTT) could not be performed in all of the general population in this national survey. Moreover, an OGTT is not recommended for subjects without any risk factors for type 2 diabetes. Third, we included people with previous or current hypoglycaemic treatment and people with hypertension, which might influence the distribution of HbA1c or FPG levels. However, we found that hypoglycaemic treatment had no effect on the HbA1c cut-off value in a sensitivity analysis. Fourth, differences in thresholds might arise when the analysis was based on any DR as opposed to diabetes-specific DR. In other words, a microaneurysm could be caused from other causes than diabetes. Lastly, different statistical approaches might lead to different diagnostic thresholds. It might be difficult to determine clear cut-offs if changes in the prevalence of diabetic retinopathy tend to be linear, especially for the change point analysis. In the present study, the cut-offs from the ROC analysis were similar to those observed in the continuous decile plot; these values were also supported by the changes of the OR in the logistic regression analysis.

In summary, our study showed the association of HbA1c and FPG with the prevalence of retinopathy and provided additional evidence for diagnosing diabetes in Asian populations. Using the HbA1c and FPG cut-off values of 6.2% (44 mmol/mol) and 6.3 mmol/l, respectively, the prevalence of retinopathy increased. HbA1c had better discrimination than FPG for detecting the presence of retinopathy. A follow-up study to determine the relationship of FPG and HbA1c to the incidence of DR is needed.

Conflict of interest statement

The authors declare that there are no conflicts of interests.

Acknowledgements

We thank all participants and members of Committee of Clinical practice Guideline of Korean Diabetes Association. The members of the Committee are: N.H. Kim (Department of Internal Medicine, Korea University College of Medicine), D.H. Kim (Sanggye Paik Hospital), S.Y. Kim (Department of Internal Medicine, Chosun University School of Medicine), S.R. Kim (Department of Internal Medicine, The Catholic University of Korea), S.K. Kim (Department of Internal Medicine, CHA University School of Medicine), C.H. Kim (Department of Internal Medicine, Soonchunhyang University College of Medicine), K.H. Shim (Samsung Medical Center), M.H. Woo (Kyung Hee University Medical Center), J.H. Lee (Department of Internal Medicine, Daegu Catholic University), H.J. Lee (Department of Internal Medicine, Ewha Woman's University School of Medicine), E.K. Hong (Department of Internal Medicine, Hallym University College of Medicine), and Y.C. Hwang (Department of Internal Medicine, Kyung Hee University School of Medicine).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2014.04.003.

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