

Glycosylated Hemoglobin Threshold for Predicting Diabetes and Prediabetes from the Fifth Korea National Health and Nutrition Examination Survey

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We aimed to estimate the threshold level of glycosylated hemoglobin (HbA1c) for the fasting plasma glucose of 100 and 126 mg/dL in the Korean adult population, using the 2011 Korea National Health and Nutrition Examination Survey. A total of 4,481 participants over 19 years of age without diabetic medications and conditions to influence the interpretation of HbA1c levels, such as anemia, renal insufficiency, liver cirrhosis, and cancers, were analyzed. A point-wise area under the receiver operating characteristic curve was used to estimate the optimal HbA1c cutoff value. A HbA1c threshold of 6.35% was optimal for predicting diabetes with a sensitivity of 86.9% and a specificity of 99.1%. Furthermore, the threshold of HbA1c was 5.65% for prediabetes, with a sensitivity of 69.3% and a specificity of 71%. Further prospective studies are needed to evaluate the HbA1c cutoff point for diagnosing prediabetes and diabetes in the Korean population.

Keywords: Diabetes mellitus; Diagnosis; Hemoglobin A; Glycosylated

INTRODUCTION

Glycosylated hemoglobin (HbA1c) is a standard monitoring test for long-term glycemic control. Although a shift from glucose-based diagnosis to a HbA1c-based diagnosis may still be debated across ethnic groups [1], HbA1c has been recently recommended as one diagnostic criteria for diabetes. In Korea, HbA1c was recommended as a diagnostic criterion for diabetes in clinical practice guidelines for type 2 diabetes in 2011 [2]. Using the HbA1c levels than using the fasting plasma glucose (FPG) levels has several advantages in the diagnosis of diabetes, such as greater convenience and less day-to-day perturbations during stressful conditions [3]. However, these advantages must be balanced by the incomplete correlation be-

tween HbA1c and the average glucose in some clinical conditions, such as anemia, renal insufficiency, liver cirrhosis, and cancers [4,5]. Several studies have been performed to predict prediabetes and diabetes in nondiabetic Korean participants, using oral glucose tolerance test (OGTT)-based and HbA1c-based diagnostic criteria [6-8]. A recent epidemiological study using the data from the Korea National Health and Nutrition Examination Survey (KNHANES) has been reported [9], but this study did not exclude those conditions influencing the HbA1c levels. Using data from the 2011 KNHANES, we estimated the threshold level of HbA1c for the FPG of 100 and 126 mg/dL, traditional fasting glucose-based diagnostic criteria in the Korean adult population.

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METHODS

The KNHANES, conducted periodically by the Korea Centers for Disease Control and Prevention (KCDC) and initiated in 1998, was designed to provide comprehensive information on Koreans' health status, health behavior, and nutritional status [10]. Data from the second-year (2011) KNHANES V, including HbA1c, and fasting blood glucose, were used in this cross-sectional analysis. All laboratory data monitor laboratory performance by quality control programs to ensure that all analytical values meet acceptable standards of precision and accuracy [10].

From an initial total of 8,518 participants, 6,066 persons (2,677 men and 3,389 women) with HbA1c and fasting glucose data and who were not taking diabetic medications, were evaluated. From 6,066 persons, 1,585 were excluded for the following reasons: 82 persons had a lack of underlying disease information; 707 persons were below 18 years old; fasting time was not over 10 hours in 262 persons; 366 persons had anemia, which was defined as a hemoglobin value <130 g/L in men ($n=67$) and <120 g/L in women ($n=299$); eight persons were pregnant; the estimated glomerular filtration ratio, using the Modification of Diet in Renal Disease study equation of 14 persons, was less than 60 mL/min/1.73 m²; nine persons had liver cirrhosis; and 137 persons had any type of cancer. A total

of 4,481 persons were used in this analysis. All examination (or testing) protocols were approved by the KCDC Institutional Review Board, with each subject providing written informed consent before participating and the Institutional Review Board of Hallym University Sacred Heart Hospital reviewed and approved the study protocol. The receiver operating characteristic (ROC) curves for HbA1c were plotted, and statistical analyses were performed using the SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). *P* values of less than 0.05 were considered statistically significant.

RESULTS

The study participants included 1,992 men and 2,489 women. The mean age was 48.63 ± 16.3 years, and 55.5% were women. Their mean body mass index was 23.6 ± 3.4 kg/m², and waist circumference was 81.2 ± 10.1 cm. The fasting blood glucose was 93.9 ± 14.4 mg/dL, and HbA1c was $5.6\% \pm 0.5\%$. Other metabolic parameters were as follows: systolic blood pressure was 118.2 ± 17.0 mm Hg; diastolic blood pressure was 75.8 ± 10.4 mm Hg; total cholesterol was 192 ± 36 mg/dL; triglyceride level was 131 ± 106 mg/dL; and low density lipoprotein cholesterol was 115 ± 33 mg/dL.

Fig. 1 shows the ROC curve for HbA1c predicting prediabetes and diabetes among individuals without diabetic medi-

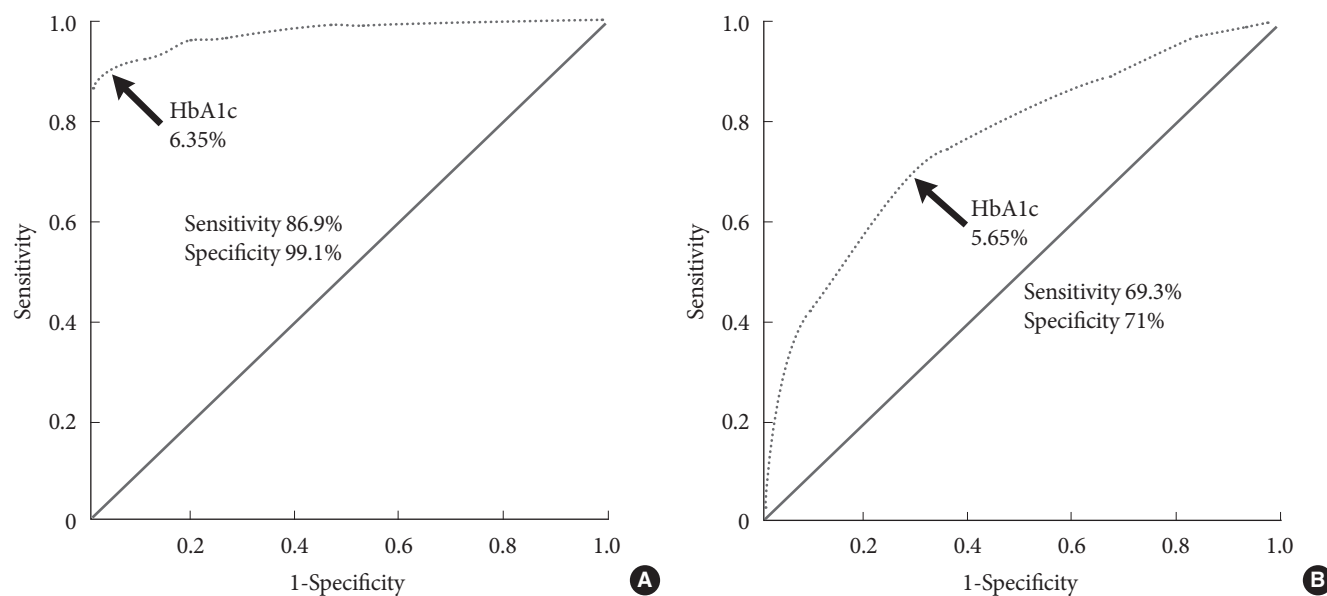


Fig. 1. Receiver operating characteristic curves for performance of glycosylated hemoglobin (HbA1c) and fasting plasma glucose corresponding to diabetes and prediabetes without diabetic medications, defined by the 2015 American Dental Association criteria among the Korean population by glucose levels. (A) Fasting plasma glucose (FPG) of 126 mg/dL. (B) FPG of 100 mg/dL.

cations. A HbA1c cutoff of 6.35% was the optimal threshold for the FPG of 126 mg/dL, with 86.9% sensitivity and 99.1% specificity (area under the curve, 0.977; 95% confidence interval [CI], 0.966 to 0.988; $P < 0.001$). A HbA1c cutoff of 6.5% produced a sensitivity of 68.8% and a specificity of 100% for a FPG of 126 mg/dL (Fig. 1A). A HbA1c cutoff of 5.65% was shown to be the optimal threshold for a FPG of 100 mg/dL, with 69.3% sensitivity and 71% specificity (area under the curve, 0.760; 95% CI, 0.741 to 0.780; $P < 0.001$). A HbA1c cutoff of 5.7% produced a sensitivity of 57.1% and a specificity of 80.7% for a FPG of 100 mg/dL (Fig. 1B).

DISCUSSION

Type 2 diabetes is a progressive disease characterized by the development or worsening of multiple chronic complications [11]. Therefore, it is important to prevent diabetes-associated complications through the early diagnosis and prevention of diabetes. This study suggests that FPG is accurately measured for the screening or diagnosis of prediabetes and diabetes because the established FPG criterion for the diagnosis of hyperglycemic states is still valid. However, the measurement of FPG is subject to some limitations. Patients for screening of diabetes must fast ≥ 8 hours, and many laboratories, including the Korean National Health Insurance Corp., measure the serum glucose [12], even though their guidelines recommend plasma. Therefore, we included HbA1c as a diagnostic criterion for prediabetes and diabetes in Korea. The Korean Diabetes Association suggests that FPG and HbA1c tests are equally reliable methods for detecting prediabetes or diabetes [2].

Several studies have been performed to examine the threshold for HbA1c for the prediction of prediabetes and diabetes in nondiabetic Korean participants [6-8]. Kim et al. [6] reported that the optimal cutoff points for HbA1c and FPG for the diagnosis of diabetes in 392 subjects with risk factors for diabetes were 6.1% (sensitivity 81.8%, specificity 84.9%) and 110 mg/dL (sensitivity 85.2%, specificity 88.5%), respectively. One hospital-based study, using data from 405 subjects without known diabetes and who underwent OGTT and HbA1c tests for the diagnosis of diabetes, showed that the HbA1c threshold of 6.1% optimally identified diabetes (sensitivity 77.8%, specificity 71.7%) [7]. Lee et al. [8] analyzed 4,616 subjects without diabetes and reported an optimal point of 6.1% HbA1c to diagnose diabetes, with a sensitivity of 63.8% and specificity of 88.1% and a HbA1c cutoff of 5.7% for the identi-

fication of prediabetes (sensitivity 48.6%, specificity 65.7%). These hospital-based or community-based studies showed that the HbA1c threshold is lower than the American Dental Association (ADA) criterion.

In the recent epidemiological study based on the 2011 KNHANES, a HbA1c threshold of 6.1% and 6.5% produced sensitivities of 85.2% and 67.7% and specificities of 90.5% and 98.0% for a FPG of 126 mg/dL, respectively [9]. These findings were similar to those reported previously in several Korean cohort studies. Based on the high specificity of a HbA1c cutoff of 6.5%, Kim et al. [9] reported that the current diagnostic criteria of HbA1c $\geq 6.5\%$ might be acceptable in the Korean adult population. However, our data in the 2011 KNHANES that excluded these conditions to influence the interpretation of HbA1c levels, such as anemia, renal insufficiency, liver cirrhosis, and cancers, demonstrated that the HbA1c cutoff points for the diagnosis of diabetes were 6.35% with a sensitivity and specificity of 86.9% and 99.1%, respectively. Our findings showed that the HbA1c level for the diagnosis of diabetes in Korea might be lower than the ADA criterion, although the HbA1c level was slightly higher than the results in the previous community- or hospital-based and national representative studies of the Korean adult population [11].

The epidemiological data showed a strong correlation between HbA1c and the risk of diabetic retinopathy (DR), as seen with the FPG and 2-hour plasma glucose (PG) levels, as well as other microvascular complications of diabetes [13-15]. However, few representative population-based data sets are available regarding the glycemic and HbA1c thresholds for detecting DR in Asia. A recent study using data from the 2011 KNHANES showed that the overall glycemic thresholds for DR were 113.4 mg/dL for FPG and 6.2% for HbA1c. The sensitivities and specificities were 82.6% and 91.2% for FPG and 93.9% and 89.7% for HbA1c, respectively [16]. The optimal thresholds did not differ by age group. Although the KNHANES was based on cross-sectional data, this report was the first population-based nationwide study for the associations of FPG and HbA1c with DR in a Korean population, and it was suggested that the current diabetes diagnostic values for FPG and HbA1c based on DR may be lower for the Korean population, similar to the opinion of our study [16].

There are several limitations in this study. First, the KNHANES was based on cross-sectional data. Second, the information for hemoglobinopathy to influence the interpretation of HbA1c levels was not included in this study, even

though the prevalence of hemoglobinopathy is low in Korea. Finally, 2-hour PG levels during an OGTT were not included in this analysis, although an OGTT could not be performed in the KNHANES.

In conclusion, this study shows that the measurement of the HbA1c may be efficient in identifying participants without diabetic medications with a HbA1c cutoff of 6.35% being highly specific and sensitive for the diagnosis of diabetes and a HbA1c of 5.65% being a reasonable threshold for prediabetes. Further prospective studies are needed to evaluate the HbA1c cutoff point for diagnosing prediabetes and diabetes in the Korean population.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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