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SHORT REPORT

Impact of hemoglobin A1c-based criterion on diagnosis of prediabetes: The Korea National Health and Nutrition Examination Survey 2011

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ABSTRACT

To examine the impact of hemoglobin A1c (HbA1c) criterion on the diagnosis of prediabetes in Koreans, we analyzed nationally representative cross-sectional data of 5,845 Korean adults aged ≥20 years from the Fifth Korea National Health and Nutrition Examination Survey 2011. Standardized prevalence rates of prediabetes in Korean adults by fasting plasma glucose (FPG; 5.6–6.9 mmol/L), HbA1c (5.7–6.4% [39–46 mmol/mol]), and combined criteria were 16.9, 28.4 and 33.8%, respectively. Among the subjects with prediabetes, 16% met FPG criteria only, 55% met HbA1c criteria only and 29% met both criteria. Prediabetic subjects who met HbA1c criteria only were significantly older, more likely to be women, and had lower hemoglobin and serum iron concentrations, whereas those who met FPG criteria only had higher body mass index, waist circumference, systolic and diastolic blood pressure. In conclusion, introduction of HbA1c criterion markedly increased the prevalence of prediabetes in Koreans, and the two criteria identified people with different characteristics.

INTRODUCTION

Since the introduction of hemoglobin A1c (HbA1c) criteria to diagnose diabetes mellitus, HbA1c levels above the laboratory 'normal' range, but below the diagnostic cut-point for diabetes (5.7–6.4% [39–46 mmol/mol]), are categorized as 'increased risk for diabetes' or 'prediabetes'[1]. However, epidemiological studies have shown significant discordance between HbA1c and glucose-based tests for defining prediabetes[2,3]. Furthermore, the degree of diagnostic agreement of HbA1c criteria with fasting glucose criteria might be different across ethnic groups and populations[4–6]. Currently, the Korean Diabetes Association also recommends the use of HbA1c (5.7–6.4% [39–46 mmol/mol]) in identifying a 'high-risk group for diabetes' along with fasting or post-load glucose levels. In our previous studies using private health check-up data in Koreans, there were considerable discordances in detecting subjects with diabetes and prediabetes between the fasting plasma glucose (FPG)- and HbA1c-based criteria, and HbA1c criteria had lower sensitivity compared with FPG criteria[7,8]. However, we could not generalize the results to the whole Korean population, because the subjects were not a random sample of the general population.

In the present study, we examined the difference in prevalence of prediabetes using FPG and HbA1c criteria in a nationally representative sample of the Korean population. In addition, we analyzed the factors associated with the discordance between FPG- and HbA1c-based diagnosis of prediabetes.

MATERIALS AND METHODS

We obtained data from the second year (2011) of the Fifth Korea National Health and Nutrition Examination Survey (KNHANES V-2), a cross-sectional and nationally representative survey of the non-institutionalized civilian population carried out by the Korea Centers for Disease Control and Prevention[9]. Participants were randomly selected using a stratified, multistage probability sampling design to represent the national population of South Korea. Written informed consent was obtained from all participants, and the study procedures were carried out in accordance of the Declaration of Helsinki. Details of information about the KNHANES are provided elsewhere[10]. Among the 6,500 participants aged ≥20 years, 5,845 individuals (2,512 men and 3,333 women) were included in the

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present analysis after excluding 655 individuals with missing data for FPG or HbA1c. Prediabetes was defined by FPG (5.6–6.9 mmol/L), HbA1c (5.7–6.4% [39–46 mmol/mol]) and combined criteria (FPG 5.6–6.9 mmol/L or HbA1c 5.7–6.4% [39–46 mmol/mol]).

Anthropometric and blood pressure measurements were carried out by trained personnel. Bodyweight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Blood pressure (BP) was measured on the right arm in a sitting position after a 5-min rest using a mercury sphygmomanometer. Blood samples were obtained in the morning after an overnight fast of at least 8 h. FPG was measured by the hexokinase method using an autoanalyzer (Hitachi Automatic Analyzer 7600, Tokyo, Japan). HbA1c was measured by high-performance liquid chromatography (HLC-723G7; Tosoh, Tokyo, Japan), which has been aligned to the Diabetes Control and Complications Trial reference standard and certified by the National Glycohemoglobin Standardization Program[11].

Statistical analyses were carried out using the SPSS® 14.0 software package (SPSS Inc., Chicago, IL, USA). To provide nationally representative prevalence estimates, a sample weight was assigned for the participating individuals for adjustment to population structure reflecting the unequal probability of selection and non-response. Unpaired Student's *t*-test or χ^2-test were used to compare groups. The receiver operating characteristic curve was plotted to determine the optimal cut-off point of HbA1c in reference to FPG-based prediabetes. *P*-values <0.05 were considered statistically significant.

RESULTS

Among the 5,845 participants, 483 individuals had previously diagnosed diabetes and 263 participants were newly diagnosed as diabetes by FPG or HbA1c tests. After adjustment for population structure, the national estimated prevalence of diabetes in Korean adults aged ≥20 years was 10.7%. Among the 5,099 participants without diabetes, 985 (19.3%) individuals were classified as prediabetes by FPG criteria, 1,854 (36.4%) by HbA1c criteria and 2,198 (43.1%) by combined criteria. After adjustment for population structure, the national estimated prevalence of prediabetes in Korean adults aged ≥20 years by FPG, HbA1c, and combined criteria were 16.9% (men 20.4%, women 13.4%), 28.4% (men 29.1%, women 27.7%) and 33.8% (men 36.1%, women 31.6%), respectively. Therefore, the national prevalence of prediabetes increased by twofold by including the new HbA1c criteria in addition to FPG criteria. This trend was similar across all age groups, although the prevalence of prediabetes was getting higher with increasing age (Figure 1).

Among the 2,198 participants with prediabetes, 344 (16%) met FPG criteria only (FPG only group), 1,213 (55%) met HbA1c criteria only (HbA1c only group) and 641 (29%) met both criteria. When we compared the prediabetes by FPG only and HbA1c only groups, the HbA1c only group was significantly older, more likely to be women, and had significantly lower hemoglobin, serum iron and ferritin concentrations

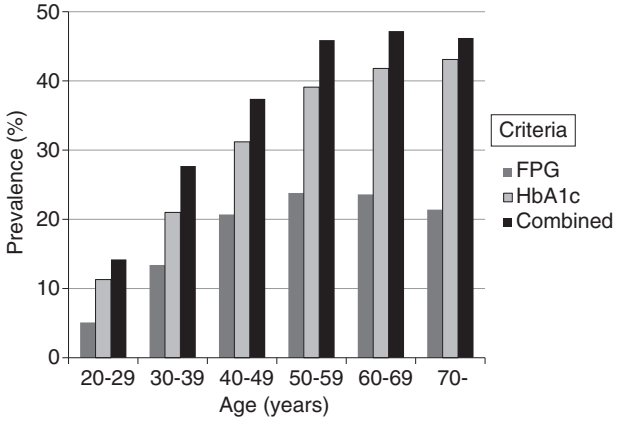

Figure 1 | Prevalence of prediabetes in different age groups by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) criteria. FPG criteria, FPG 5.6–6.9 mmol/L; HbA1c criteria, HbA1c 5.7–6.4% (39–46 mmol/mol); combined criteria, FPG 5.6–6.9 mmol/L or HbA1c 5.7–6.4% (39–46 mmol/mol).

($P < 0.001$ for all; Table 1). In contrast, the FPG only group had significantly higher body mass index, waist circumference, systolic BP and diastolic BP ($P < 0.001$ for all). When we analyzed the data for men and women separately, the results were basically similar, although the differences in systolic BP and ferritin in women did not reach statistical significance. Exclusion of participants with anemia (hemoglobin <130 g/L in men [$n = 107$] and <120 g/L in women [$n = 433$]) did not change the results significantly (data not shown). The optimal cut-off point of HbA1c for prediabetes in reference to classical FPG-based prediabetes was 5.7% (39 mmol/mol), with sensitivity and specificity of 68 and 61%, respectively (Figure 2).

DISCUSSION

The present analysis of Korean national data showed that the prevalence of prediabetes increased markedly by introducing HbA1c criterion. Our results are different from those of the US National Health and Nutrition Examination Survey (NHANES), which showed that the same HbA1c criterion (5.7–6.4% [39–46 mmol/mol]) resulted in substantially lower prevalence of prediabetes than prevalence estimated from FPG criterion (5.6–6.9 mmol/L)[3,12]. In contrast, the present results are in agreement with studies from southern Europe[13] and China[14], which showed that a larger proportion of prediabetes was identified by HbA1c measurement using the same criterion. This could be due to ethnic differences, as HbA1c levels are reported to be higher in Asian people compared with white people in the USA with impaired glucose tolerance after adjustment for glycemia[4]. In fact, linear regression analysis of our data showed that the HbA1c value corresponding to FPG 5.6 mmol/L was 5.8%. However, we used the cut-off point of 5.7% according to the American Diabetes Association criteria for international comparison of the prevalence. In a previous study using private health check-up data in Koreans, this HbA1c criterion had

Table 1 | Clinical characteristics of newly diagnosed patients with prediabetes who met fasting plasma glucose criteria only and those who met hemoglobin A1c criteria only

Whole population	Prediabetes by FPG (n = 344)	Prediabetes by HbA1c (n = 1,213)	P-value
Age (years)	46.4 ± 13.4	51.0 ± 15.6	<0.001
Sex, male/female (%)	64/36	47/53	<0.001
BMI (kg/m^2)	24.8 ± 3.6	23.9 ± 3.3	<0.001
Waist circumference (cm)	84.7 ± 10.2	82.2 ± 9.6	<0.001
Systolic BP (mmHg)	122 ± 17	118 ± 16	<0.001
Diastolic BP (mmHg)	80 ± 11	76 ± 10	<0.001
Fasting glucose (mmol/L)	5.8 ± 0.3	5.0 ± 0.3	<0.001
HbA1c,% (mmol/mol)	5.4 ± 0.2 [36 ± 2]	5.8 ± 0.2 [40 ± 2]	<0.001
Hb concentration (g/L)	149 ± 15	139 ± 17	<0.001
Iron (μmol/L)	22.7 ± 10.0	19.5 ± 8.2	<0.001
Ferritin (pmol/L)	274 ± 278	182 ± 175	<0.001
Total cholesterol (mmol/L)	5.07 ± 0.91	5.12 ± 0.93	0.090
Triglycerides (mmol/L)	1.86 ± 1.82	1.61 ± 1.20	0.058
Men	**Prediabetes by FPG (n = 201)**	**Prediabetes by HbA1c (n = 456)**	**P-value**
Age (years)	45.0 ± 12.8	47.8 ± 15.6	0.008
BMI (kg/m^2)	25.0 ± 3.7	24.1 ± 3.2	0.009
Waist circumference (cm)	86.9 ± 10.0	85.0 ± 9.2	0.016
Systolic BP (mmHg)	123 ± 15	119 ± 14	<0.001
Diastolic BP (mmHg)	82 ± 10	78 ± 10	<0.001
Fasting glucose (mmol/L)	5.8 ± 0.3	5.1 ± 0.3	<0.001
HbA1c,% (mmol/mol)	5.4 ± 0.2 [36 ± 2]	5.8 ± 0.2 [40 ± 2]	<0.001
Hb concentration (g/L)	156 ± 11	151 ± 11	<0.001
Iron (μmol/L)	24.6 ± 10.4	22.7 ± 8.4	0.001
Ferritin (pmol/L)	359 ± 293	264 ± 203	<0.001
Total cholesterol (mmol/L)	4.98 ± 0.87	5.09 ± 0.87	0.471
Triglycerides (mmol/L)	2.09 ± 2.14	1.82 ± 1.42	0.063
Women	**Prediabetes by FPG (n = 143)**	**Prediabetes by HbA1c (n = 757)**	**P-value**
Age (years)	49.0 ± 14.0	53.8 ± 15.0	<0.001
BMI (kg/m^2)	24.4 ± 3.2	23.8 ± 3.4	0.005
Waist circumference (cm)	80.8 ± 9.2	79.9 ± 9.3	0.049
Systolic BP (mmHg)	121 ± 19	118 ± 17	0.195
Diastolic BP (mmHg)	77 ± 11	74 ± 10	0.014
Fasting glucose (mmol/L)	5.8 ± 0.2	5.0 ± 0.3	<0.001
HbA1c,% (mmol/mol)	5.4 ± 0.2 [36 ± 2]	5.8 ± 0.2 [40 ± 2]	<0.001
Hb concentration (g/L)	134 ± 9	128 ± 13	<0.001
Iron (μmol/L)	19.7 ± 8.2	16.7 ± 7.1	0.001
Ferritin (pmol/L)	125 ± 165	111 ± 89	0.110
Total cholesterol (mmol/L)	5.23 ± 0.97	5.16 ± 0.99	0.460
Triglycerides (mmol/L)	1.43 ± 0.88	1.41 ± 0.94	0.369

BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; Hb, hemoglobin; HbA1c, hemoglobin A1c.

lower sensitivity in detecting patients with prediabetes compared with the FPG criterion[8]. The reason for such discrepancy is not clear at present, but differences in subject selection and methods of measurement might be responsible. This national survey data from randomly selected subjects using stratified, multistage probability sampling could be representative of the general Korean population. In addition, the measurements of glucose and HbA1c were carried out in a certified central laboratory with strictly standardized methods.

There was considerable discordance in diagnosing patients with prediabetes between the FPG- and HbA1c-based criteria. Individuals with prediabetes who met the HbA1c criteria only

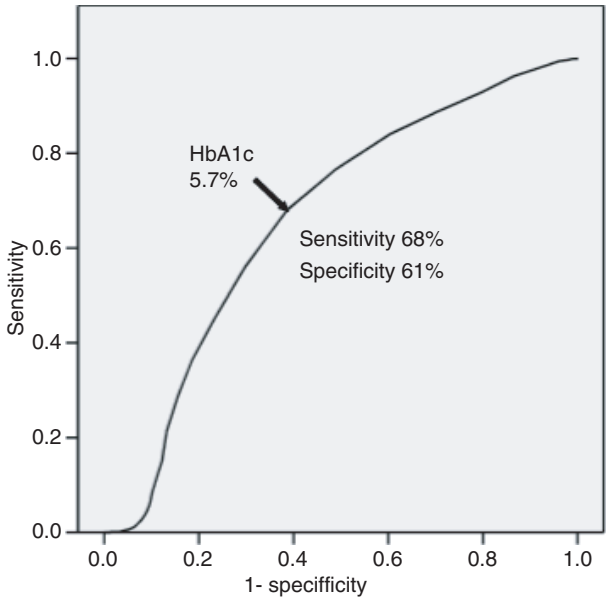

Figure 2 | Receiver operating characteristic curve for hemoglobin A1c (HbA1c) cut-off point for prediabetes in reference to fasting plasma glucose-based prediabetes (impaired fasting glucose).

were significantly older, more likely to be women, and had lower hemoglobin and serum iron concentrations. Similar findings have been observed when we compared the HbA1c criteria and FPG criteria in the diagnosis of diabetes[7] or in the definition of dysglycemia for metabolic syndrome[15]. These are consistent with the report that HbA1c concentrations increase with age in populations without diabetes[16]. Previous studies suggest that iron deficiency anemia also affects the HbA1c levels[17,18]. In a study of young Indians, a high prevalence of prediabetes diagnosed by HbA1c has been attributed to iron deficiency anemia[19]. However, this possibility is less likely in the present study, since exclusion of patients with anemia did not change the results significantly. This result suggests that low serum iron within the normal range is associated with increased HbA1c levels, although the mechanisms are not clear.

The strength of the present study was that the participants were randomly selected using a stratified, multistage probability sampling design to represent the national population. In addition, the health examination was carried out using standardized protocol by trained personnel, and biochemical measurements were carried out in a central laboratory with strict quality control. The major limitations were lack of oral glucose tolerance test and only single measurements of FPG or HbA1c, which might have introduced a misclassification bias. Second, the cross-sectional study design limited the ability to examine the performance of HbA1c in predicting diabetes and its complications. Increased detection of prediabetes could contribute to preventing or delaying the progression to diabetes and development of its complications by early intervention, but might also cause an increase of initial healthcare cost, although not in the long-term[20], and psychosocial burden. Prospective studies are required to define the high-risk group in which intensive screening and early intervention will be most beneficial.

In conclusion, introducing additional HbA1c criterion causes a marked increase of prevalence of prediabetes in Koreans, and it identifies people with different characteristics compared with the FPG criterion. Prospective studies are required to establish an optimal HbA1c cut-off point, and guidelines for screening and management of prediabetes in the general population.

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The authors declare no conflict of interest.

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