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Optimal glycated albumin cutoff value to diagnose diabetes in Korean adults: A retrospective study based on the oral glucose tolerance test

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ABSTRACT

Introduction: Glycated albumin (GA) reflects short-term status of glycemic control. We suggest a GA cut-off value to diagnose pre-diabetes and diabetes in Korean adults. In addition, we compared the performance of GA for the diagnosis of diabetes with that of glycated hemoglobin (A1c).
Materials and methods: A total of 852 subjects (498 males, 354 females) aged 20 to 83 years (mean: 52.5 years) were enrolled. A 75-g oral glucose tolerance test (OGTT) was performed and A1c and GA were measured.
Results: In these enrolled subjects, 88% have glucose intolerance status (pre-diabetes or diabetes). The GA concentrations corresponding to fasting plasma glucose (FPG) of 7.0 mmol/l, 2-h plasma glucose during OGTT (PPG2) ≥ 11.1 mmol/l, and A1c ≥ 6.5% were 14.6%, 13.7%, and 14.7%, respectively. A meta-analysis of three GA cutoffs revealed a GA cutoff for diabetes of 14.3%. When A1c is used in combination with FPG, the sensitivity and specificity for the diagnosis of OGTT-based diabetes were 72.16% (95% CI: 66.6–72.2) and 96.4% (95% CI: 94.4–97.7), respectively. With the newly developed GA cutoff of 14.3%, GA combined with FPG resulted in a sensitivity and specificity of 77.5% (95% CI: 72.17–82.0) and 89.9% (95% CI: 87.1–92.2), respectively.
Conclusions: A GA cutoff of >14.3% is optimal for the diagnosis of diabetes in Korean adults. The measurement of FPG and GA may detect diabetes earlier than the measurement of FPG and A1c.

1. Introduction

There is little controversy on the use of fasting plasma glucose concentrations as the gold standard diagnostic criteria for diabetes or, much less frequently, the use of the 2-h OGTT and the glycated hemoglobin (A1c) measurement. Of these components for diagnosing diabetes, the International Expert Committee states that A1c is an alternative tool but not superior to blood glucose, leaving it up to health-care professionals to decide which test to use on an individual basis [1]. However, much debate and controversy remains on precisely which test, either A1c or plasma glucose, is optimal for diagnosing diabetes [2]. The argument for and against the use of A1c measurement may reflect the interesting epidemiology of diabetes, the pathophysiological abnormalities that occur during the development of diabetes, its relevance to chronic diabetic complications, etc. [2]. In this unsettled situation regarding the best diagnostic tool for diabetes, the usefulness of glycated albumin (GA) has been gaining popularity as an intermediate glycemic index for glycemic monitoring and its association with diabetic atherosclerosis [3,4]. In light of the growing evidence on the pathophysiological and clinical relevance of GA in subjects with type 2 diabetes [5,6], the potential for GA as a diagnostic tool for type 2 diabetes in Japanese and Chinese populations has sparked ongoing investigation [7,8]. We hypothesized that the diagnostic cut-off value for GA might be different for different ethnicities and that the establishment of a cutoff value might be useful for future studies of chronic diabetic complications.

Abbreviations: GA, glycated albumin; OGTT, oral glucose tolerance test; PPG2, 2-h plasma glucose during OGTT; HOMA, homeostasis model assessment; NGSP, National Glycated Hemoglobin Standard Program.

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2. Materials and methods

2.1. Study population

Study subjects were recruited from outpatient clinics at 4 major referral centers (Kyung Hee University Hospital at Gangdong, Kangbuk Samsung Hospital, Samsung Medical Center, and Severance Hospital, Seoul, Republic of Korea) between March 2011 and February 2013. During this period, a total of 959 subjects who had data regarding GA and A1c and received an oral glucose tolerance test (OGTT) were recruited. To eliminate the effects of glucose-lowering agents on serum GA and A1c concentrations, we limited the study subjects to those who were free of oral hypoglycemic drugs including insulin. Among those patients, 31 subjects were excluded because A1c or OGTT data was not entirely available for the analysis. In addition, 89 subjects were excluded from this study due to one of the following: (1) hemoglobin concentration < 12 g/dl (n = 38); (2) chronic kidney disease ≥ stage 3 (n = 11); (3) active thyroid disease (n = 34); (4) liver cirrhosis (n = 5); and (5) nephrotic syndrome (n = 6). Two foreign subjects were also excluded. Finally, a total of 852 subjects (498 males and 354 females) aged 20 to 83 years (mean age: 52.5 years) were enrolled in the study. Ethics approval for the study protocol and analysis of the data was obtained from the Institutional Review Board of each hospital.

2.2. Clinical and laboratory examination

At baseline, a complete physical examination was performed, and personal medical history, medications, and lifestyle factors, including cigarette smoking and alcohol consumption were determined. Smoking was classified into three groups (current smoker, ex-smoker, and never smoker) and alcohol intake was defined as >3 drinks per day (>30 g ethanol/day). Blood pressure was measured by an automatic device on the right arm after a 5-min rest interval with the patient in a seated position. Weight and height were measured in the morning with subjects wearing light clothing and no shoes.

A 75-g OGTT was performed after an overnight fast of 12 to 14 h. Subjects ingested 75 g of glucose, and blood samples were taken at 0, 30, 60, 90, and 120 min for the plasma glucose assay and serum insulin concentrations were measured at 0 and 30 min. All biochemical measurements including GA and A1c concentrations were determined at the time of blood sampling. Serum total cholesterol, triglycerides, HDL cholesterol, and directly-measured LDL cholesterol concentrations were determined using an autoanalyzer. Serum GA was determined by an enzymatic method using an albumin-specific proteinase, ketoamine oxidase, and albumin assay reagent (LUCICA GA-L, Asahi Kasei Pharma Co.) using a Hitachi 7699 Pmodule autoanalyzer (Hitachi Instruments Service) and the CV was 1.43%. A1c was measured by high-performance liquid chromatography (HPLC) using a Variant II Turbo (Bio-Rad Labs). The reference intervals of A1c were between 4.0 and 6.0%, while those of GA were between 11.0 and 16.0%.

In this study, diabetes was defined by the presence of one of the following: (1) fasting plasma glucose (FPG) concentrations ≥ 7.0 mmol/l; (2) 2-h plasma glucose (PPG2) ≥ 11.1 mmol/l during OGTT; or (3) A1c concentrations ≥ 6.5%. Normal glucose tolerance was defined by the presence of all of the following: (1) fasting plasma glucose concentrations < 5.6 mmol/l; (2) 2-h plasma glucose < 7.8 mmol/l during OGTT; and (3) A1c concentrations < 5.7%. Pre-diabetes was defined as the subjects who have neither normal glucose tolerance nor diabetes [9,10]. The HOMA (homeostasis model assessment) model was used to estimate the degree of insulin resistance and β-cell function from fasting glucose and insulin concentrations. Insulin resistance (IR) was estimated using the HOMA-IR, defined as [fasting insulin (μU/ml) × fasting glucose (mmol/l)] / 22.5. HOMA-B was calculated using (20 × fasting insulin) / (fasting glucose − 3.5), and used to represent β-cell function [11]. The reference ranges for insulin, C-peptide and HOMA are not reported by the researchers' institution.

2.3. Statistical methods

All data are expressed as the mean ± SD or as proportions, except for skewed variables, which are presented as the median (interquartile range, 25%–75%). Differences among groups were tested by ANOVA or the Kruskal–Wallis test for continuous variables, and the linear-by-linear association test was used for categorical variables. Spearman correlation coefficients were calculated to evaluate the associations between GA and glucose, A1c, and HOMA values. To determine the relationship between serum GA and FPG, PPG2, and A1c concentrations, we fitted the two linear regression models and obtained changing points of serum GA according to deterioration of glucose tolerance. To determine the optimal serum GA cutoffs for the diagnosis of pre-diabetes and diabetes, we predicted the GA concentrations and 95% confidence intervals (CIs) corresponding to a FPG value of between 5.6 and 7.0 mmol/l. The same approach was used to predict serum GA cutoffs for PPG2 and A1c. Thereafter, we meta-analyzed three GA cutoffs for pre-diabetes from FPG, PPG2, and A1c concentrations with a fixed effect model, and similarly, the serum GA cutoff for the diagnosis of diabetes was estimated using a random effect model. In addition, the cutoff value of GA to diagnose diabetes was calculated by receiver operating characteristic (ROC) analysis. Analyses were performed using R ver 2.14.2 (http://www.r-project.org). P-values < 0.05 were considered statistically significant.

3. Results

The clinical characteristics of the study participants in each group according to glucose tolerance are shown in Table 1. The mean age of the study subjects was 52.5 years, and 58.5% of the participants were male. Baseline serum GA concentrations were 11.8%, 12.4%, and 17.5% in subjects with normal glucose tolerance, pre-diabetes, and diabetes, respectively (P < 0.001). In addition, GA/A1c increased from 2.20 to 2.18 to 2.41 as the glucose tolerance deteriorated from normal glucose tolerance to pre-diabetes to diabetes (P < 0.001).

Using linear regression models, the serum GA concentrations increased steeply from FPG, PPG2, and A1c concentrations of 6.6 mmol/l, 15.7 mmol/l, and 6.0%, respectively (Fig. 1a–c). To determine the suggested GA cutoffs for the diagnosis of pre-diabetes and diabetes in Korean adults, we predicted the GA concentrations that corresponded to FPG concentrations of 5.6 mmol/l and 7.0 mmol/l, respectively (GA cutoffs (95% CI): 12.4% (12.1–12.6) for pre-diabetes and 14.6% (14.2–14.9) for diabetes). The same approach was adopted to predict serum GA cutoffs for PPG2 (GA cutoffs (95% CI): 12.5% (12.3–12.7) for pre-diabetes and 13.7% (13.5–14.0) for diabetes) and A1c (GA cutoffs (95% CI): 12.5% (12.3–12.7) for pre-diabetes and 14.7% (14.4–14.9) for diabetes) (Fig. 1a–c). We then performed a meta-analysis of the three GA cutoffs for pre-diabetes from FPG (12.4%), PPG2 (12.5%), and A1c (12.5%) concentrations and finally obtained a GA cutoff for the diagnosis of pre-diabetes of 12.5% (Fig. 2a). Using the same approach, we determined a serum GA cutoff for the diagnosis of diabetes of 14.3% for Korean adults (Fig. 2b). A GA value above 14.3% is, however, also inclusive of 26% of the distribution associated with the reference range for GA (11–16%).

With this newly developed serum GA cutoff of 14.3% for diabetes, we compared the performance of GA with A1c to diagnose diabetes based on OGTT with a FPG value ≥7.0 mmol/l or a PPG2 value ≥11.1 mmol/l. Compared to A1c, the measurement of serum GA showed a higher sensitivity (66.4% vs. 52.5%), but lower specificity (88.3% vs. 95.1%) in predicting a PPG2 concentration of >11.1 mmol/l. When FPG and A1c cutoffs were used together, the sensitivity and specificity for the OGTT-based diabetes were 72.16% (95% CI: 66.6–72.2) and 96.4% (95% CI: 94.4–97.7), respectively. When the measurement of GA cutoff was combined with FPG cutoff, the sensitivity and specificity for the detection of OGTT-based diabetes were 77.5% (95% CI: 72.17–82.0) and 89.9% (95% CI: 87.1–92.2), respectively (Table 2).