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Glycated albumin as a diagnostic tool for diabetes in a general Japanese population

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ABSTRACT

Objective. Diabetes mellitus is a major cause of cardiovascular, kidney, neurologic, and eye diseases, and may be preventable in some cases by lifestyle modification. Screening tests for diabetes mellitus include fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c). Our objective was to evaluate the utility of plasma glycated albumin (GA) in the diagnosis of diabetes mellitus.

Design and methods. A cross-sectional, community-based population study of 908 non-diabetic Japanese residents was conducted. Of these subjects, 176 with FPG value between 5.5 and 6.9 mmol/l, and an HbA1c level of <6.5% received an oral glucose tolerance test (OGTT).

Results. The OGTT results were used for the diagnosis of diabetes mellitus using World Health Organization criteria. Receiver operating characteristic (ROC) analyses demonstrated that optimal threshold values for the diagnosis of diabetes in this population were 15.2% for GA and 5.9% for HbA1c, respectively. Using these cutoff levels, the sensitivity of GA at 62.1% for detecting diabetes was the same as that of HbA1c. However the specificity for GA for detecting diabetes was 61.9%, while for HbA1c it was higher at 66.7%.

Conclusions. Our results indicate that the measurement of glycated albumin may serve as a useful screening test for diabetes in a general Japanese population.

1. Introduction

Diabetes mellitus is rapidly increasing, and the International Diabetes Federation estimates that 522 million people worldwide will have diabetes by 2030 [1]. According to large-scale epidemiological studies, large glucose fluctuations are likely to cause macrovascular diseases even at early stages of glucose intolerance [2,3]. Prevention, early diagnosis, and

Abbreviations: WHO, World Health Organization; HbA1c, glycated hemoglobin; GA, glycated albumin; OGTT, oral glucose tolerance test; KOPS, Kyushu and Okinawa Population Study; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; 2 h-PG, 2 hour postprandial plasma glucose; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; NGT, normal glucose tolerance; BMI, body mass index; ROC, receiver operating characteristic; AUC, area under the ROC curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidential interval; ARIC, Atherosclerosis Risk in Communities.

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intervention may be effective for reducing the incidence of cardiovascular events [4,5]. To diagnose diabetes and manage glycemic control, accurate and precise diagnostic and predictive biomarkers are necessary [6].

Glycated proteins are increased in diabetic patients compared with non-diabetic subjects. The American Diabetes Association and the World Health Organization (WHO) have proposed the measurement of glycated hemoglobin (HbA1c) as a diagnostic tool [7]. As the average lifespan of erythrocytes is approximately 120 days, an HbA1c level reflects a glycemic control state over the prior several months. The advantages of HbA1c are that it does not require special preparation and that it can be measured at any time of day. The disadvantages are that the assay requires whole blood, and values are affected by a shortened red blood lifespan as observed in patients with anemia, hepatic cirrhosis, and hemoglobinopathies. Under such conditions HbA1c may be inaccurate and unsuitable as a marker of glycemic control [8,9].

As the half-time of serum albumin (about 17 days) is considerably shorter than that of erythrocytes, serum glycated albumin (GA) reflects a shorter-term glycemic control (about 2–3 weeks) as compared with HbA1c [10]. GA has more rapid and greater changes than HbA1c. Therefore GA may be more useful to document treatment effects when initiating or changing medications for glucose control [11–13]. GA has also been shown to be accurate for assessing glycemic control in patients with anemia and hemoglobinopathies, as well as those on hemodialysis [14–16]. Moreover GA may have an important nephropathogenic role that might be therapeutically addressed independently of glycemic status [17].

Recently an easy to use, highly sensitive enzymatic assay for measuring GA has been developed and approved for clinical use in Japan [18]. We have previously reported a relationship between GA levels and diagnosis of diabetes and a cut-off level to diagnose diabetes was 15.5% [19]. Moreover we have reported a relationship between GA levels and the degree of carotid intimal medial thickness. GA values >15.5% were associated with subclinical atherosclerosis [20]. Other investigators have reported that GA may serve as a better indicator of glycemic fluctuations and has a better correlation with the severity of cardiovascular disease than HbA1c [21–23].

The aim of this large, cross-sectional, Japanese community-based population study was to verify the utility of GA as a screening and diagnostic tool for the early stage of diabetes as part of a follow-up medical examination using an oral glucose tolerance test (OGTT).

2. Methods

2.1. Study Population and Design

The study began in 2004 as a survey of the incidence of macrovascular events associated with lifestyle-related diseases among the general population as a part of the Kyushu and Okinawa Population Study (KOPS) [19,20]. This substudy was an evaluation of residents in two suburban areas: Iki City, an isolated island in southwestern Japan with about 28,400 residents, and Hoshino village, a rural, mountainous village with about 3300 residents. It is our impression that the lifestyle habits in terms of diet and activity patterns in these two areas are similar to those of other parts of Japan. The participants were notified, by local newspaper and public announcements, of a free annual health examination given by our department. To ensure the validity of the data, all doctors who participated in the study were staff members of the department of General Internal Medicine of Kyushu University Hospital who had been trained with regard to the study protocol and the medical procedures. This study was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000. The study was approved by the Kyushu University Hospital Ethics Committee, and written informed consent was obtained from all residents prior to the examination.

2.2. Epidemiological Study

We screened 1057 residents (348 men, 709 women, and age range 24–79 years) who participated in our health examinations in 2010 and 2011. All underwent a medical evaluation and were interviewed about their personal and family medical history and lifestyle-related habits. All had their blood drawn at our health examinations and had their levels of GA, HbA1c, fasting plasma glucose (FPG), serum insulin, and other hematological and other biochemical tests measured. The following participants were excluded from our analysis: 1) 11 participants because of insufficient data, 2) 99 participants because of the presence of viral chronic hepatitis, based on being seropositive for hepatitis B surface antigen and/or anti-hepatitis C virus antibody, having thyroid disease, being anemic, or having chronic renal disease, since these disorders are known to influence values of GA and/or HbA1c, and 3) 39 participants because of having a prior history of diabetes and/or receiving treatment for diabetes. After these exclusions, data on 908 participants (291 men, 617 women) with a median age 59 years, were available for analysis (Fig. 1).

Chronic renal disease was defined as an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73 m^2 or the presence of macro-albuminuria. eGFR was calculated using the following formula proposed by the Japanese Society of Nephrology: 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if women) [24]. Macro-albuminuria was considered positive when the dipstick test (Ames dipstick; Bayer Medical, Tokyo, Japan) for spot urine was positive, corresponding to a urinary protein level of over 300 mg/l. Common laboratory tests were included in the examination, as outlined below.

2.3. Glucose Tolerance Testing

As shown in Fig. 1, of the 908 participants in our epidemiological study, 232 participants were selected for an OGTT based on a fasting plasma glucose level between 5.5 and 6.9 mmol/l, and an HbA1c level under 6.5%. Of these eligible participants, 176 (75.9%) received an OGTT about 3 months later. The OGTT was done following a standard protocol after at least 8 hours of overnight fasting. All subjects received 75 grams of glucose orally, and had blood samples drawn at baseline, 60 minutes, and 120 minutes after the glucose challenge. Levels of GA, HbA1c, serum high-density and low-density lipoprotein