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# A comparison of glycated albumin and glycosylated hemoglobin for the screening of diabetes mellitus in Taiwan

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ABSTRACT

*Objective:* Glycated albumin (GA) values reflect an average plasma glucose level over approximately 2–4 weeks, and the assay is stable and can be run on serum or plasma. The aim of this study was to determine the universality and the clinical utility of GA in screening for diabetes mellitus.
*Methods:* Subjects consisted of 2192 male and female residents in Yi-lan County, Northern Taiwan (mean age 60.1 years), of whom 54.2% (n = 1188) had previously been diagnosed and treated for diabetes. Fasting blood samples were obtained to measure HbA1c, plasma glucose, serum GA, insulin, and measures of kidney and liver function. The reference values for these parameters were determined. Data from patients with diabetes and non-diabetic controls were also compared.
*Results:* Mean GA values were 13.8% in controls and 18.1% in diabetic subjects (31.2% higher, $p < 0.0001$), while mean HbA1c values were 5.6% in controls and 7.2% in diabetic subjects (29.2% higher, $p < 0.0001$). The 95th percentile values for GA and HbA1c in controls were 16.1% and 6.2%, respectively. Our suggested GA and HbA1c cut-points for prediabetes at the 75th percentile of the normal population would be 14.6% and 5.8%, respectively. For both parameters, values greater than these cut-points provided a reasonable degree of specificity and sensitivity for risk of having diabetes, while a GA value of 16.5% corresponds to an HbA1c level of 6.5%, diagnostic of diabetes.
*Conclusion:* These data indicate that GA values can be used as a surrogate parameter for HbA1c in screening for prediabetes and diabetes mellitus.



## 1. Introduction

Diabetes is pandemic worldwide, and is one of the most important risk factors for atherosclerotic cardiovascular disease and kidney failure [1,2]. In Taiwan, diabetes is the fourth leading cause of mortality after cancer, coronary heart disease, and stroke [3]. The estimated number of patients with diabetes in 2013 was 1.721 million (7% of the total population of Taiwan [4]. The prevalence of diabetes in Taiwan is increasing each year by about 8%, especially in the elderly population (age > 70 years), but also in the

*Abbreviations:* ALT, Alanine aminotransferase; XGI, Alpha-Glucosidase Inhibitor; BG, Biguanides; CRE, Creatinine; DM, Diabetes Mellitus; DPP-4, Dipeptidyl peptidase-4; FPG, Fasting Plasma Glucose; GA, Glycated Albumin; PRC, People's Republic of China; ROC, Receiver Operating Characteristic; SU, Sulfonylurea; TZD, Thiazolidinedione; TC, Total Cholesterol; TG, Triglyceride; UACR, Urine Albumin-to-Creatinine Ratio.

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younger population (<40 years).

Since 1995, the Taiwan government has been providing medical insurance to all citizens [5]. In this insurance system physicians are required to prescribe medicines for their patients according to a standardized algorithm for diabetes originally referred to the ADA/EASD guideline in 2008 [6,7]. Metformin as a biguanide (BG) is the first line of therapy, and should be prescribed after at least 3 months of lifestyle intervention including diet and exercise. Thereafter a sulfonylurea (SU), glinides, alpha-glycosidase inhibitor (aGI), or dipeptidyl peptidase-4 (DPP-4) inhibitors can be prescribed. When these medications are not sufficient to control the diabetes, physicians can add a third medicine chosen from one of the above medications and/or pioglitazone (a thiazolidinedione or TZD). Physicians may also consider prescribing insulin as the third medicine.

In addition to fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c) is the most widely used test worldwide for the diagnosis and treatment of diabetes mellitus [8–13]. The level of HbA1c reflects the average plasma glucose level over 3 months. Glycated albumin (GA) is a relatively new test, and GA values reflect an average plasma glucose level over approximately 2–4 weeks [14–22]. Population studies on GA have been conducted in Japan, People's Republic of China (PRC), and the United States using a newly available, fully automated, well standardized assay with excellent intraassay and interassay coefficients of variation of less than 2% [17–20]. This assay is approved for use in Japan, the Republic of Korea, the Republic of Indonesia, and PRC [21,22]. Compared with HbA1c, GA is characterized by more rapid and greater changes, and is very useful when monitoring the results of therapy when initiating or changing medications. GA can also be used in patients with anemia or hemoglobinopathies for whom the measurement of HbA1c levels may be inaccurate [17,18,23,24]. Studies using self monitoring of blood glucose and continuous glucose monitoring have found GA levels to better reflect glycemic fluctuation than HbA1c [25,26]. Moreover, GA levels were better correlated with the severity of cardiovascular disease, and were also found to be a better indicator of glycemic fluctuations than HbA1c [27].

These data indicate that GA levels are useful for the diagnosis of diabetes mellitus in populations in both Japan and the United States [17,19]. Although GA data have been accumulating in these countries, limited data are available in other countries. Therefore, the current study was designed to develop reference ranges for GA in a Taiwanese population, and to assess the universality and the clinical utility of GA in screening and the diagnosis of diabetes mellitus.

## 2. Materials and methods

The study subjects consisted of 2192 diabetic and non-diabetic individuals living in Yi-lan County in northern Taiwan. Residents of this province are native to the island of Taiwan, and are not recent immigrants from mainland China or other parts of Asia. The first diabetes shared care system was implemented in this County since 1996 [28]. All subjects agreed to participate in this study using a standard informed consent document approved by the research committees of Luodong Poh-ai Hospital, Luodong, Taiwan and the School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan. The study was carried out in 2012 and 2013.

The inclusion criteria required that study participants either have a history of diabetes mellitus (DM) and under a stable condition without any change of treatment including medication for at least 6 months (diabetic group or DM group) or have both a FPG level of less than 5.6 mmol/L (100 mg/dL) and an HbA1c levels of less than 6.5% (47.5 mmol/mol) without any treatment for diabetes mellitus at the time of a standard health examination (healthy volunteer group or control group). Originally 2370 residents participated in this study and presented data obtained at the time of their annual health examination. Based on these data, 160 subjects were excluded because of being treated for thyroid disease ($n = 33$), liver disease ($n = 62$), or kidney disease ($n = 84$). Additional 18 subjects were excluded because a serum albumin level <3.5 g/dL ($n = 6$), or having anemia (Hb < 11.0 g/dL), ($n = 14$), leaving 2192 participants available for study. Of these participants, 1004 were healthy volunteers and the other 1188 were patients with diabetes mellitus who had a history of diabetes and who being treated for this condition with either diet alone or diet and medications. A standard history about health status and medication use was obtained, and a physical examination was carried out including measurements of height, weight, and blood pressure.

The diabetic subjects were sampled at baseline, and at 3 and 6 month follow-up visits, while control subjects were sampled at baseline only. After an overnight fast of 12 h or more at all visits, blood samples were taken for the measurement of plasma glucose (hexokinase method), glycosylated hemoglobin (turbidimetric inhibition immunoassay), serum glycated albumin, and insulin levels. Other serum measurements included creatinine (CRE), liver transaminases, total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDLC), and direct low density lipoprotein cholesterol (LDLC) [29,30]. In addition morning urine samples were obtained for the measurement of micro-albumin, creatinine, and protein. All these variables except insulin were measured by automated standardized enzymatic analysis on a Cobas c501 analyzer (Hitachi Corporation, Tokyo, Japan). For this assay intra-assay and inter-assay coefficients of variations (CVs) were <3%. Insulin levels were measured by chemiluminescence assay on a Siemens Centaur automated platform with intra- and inter-assay CVs of <5%.

Serum GA levels were measured with a Lucica GA-L kit (Asahi Kasei Pharma Corporation, Tokyo, Japan). This assay uses a glycated amino acid elimination reaction with an improved enzymatic GA measurement assay. The results obtained with this assay correlated highly ($r = 0.99$) with values for GA obtained by a high-performance liquid chromatography (HPLC) assay, as previously described [17–22]. In the central laboratory at Luodong Poh-ai hospital, the GA assay had intra-assay and inter-assay CVs of 0.9 and 1.6%, respectively.

Data are shown as means ± standard deviation (SD). All statistical analyses were performed using SPSS ver.22 (IBM, Armonk, NY). Student's t-test and Chi-square test were used to compare between group differences. Receiver operating characteristic (ROC) analysis was carried out for the determination of a cut off level for diagnosing diabetes. Pearson's correlation coefficients were used for the significance of the correlationship between valuables. A P value of <0.05 was considered statistically significant.

## 3. Results

Table 1 shows the characteristics of the study subjects (1106 men and 1086 women, mean age 60.1 years). The average BMI was significantly ($p < 0.001$) higher in the DM group at 26.2 kg/m$^2$ than in the healthy volunteer group at 24.1 kg/m$^2$. While no significant gender difference was observed for HbA1c, the mean GA level was significantly higher in women than in men in the control group. No significant gender differences were observed for either GA or HbA1c in the DM group.

GA levels were also analyzed by menopausal status in women (Supplemental Table 1 for online only). In control individuals, premenopausal women had lower BMI, FPG, insulin, HbA1c, and GA values than the postmenopausal women. But in patients with diabetes mellitus, premenopausal women had a higher BMI