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# Serum glycated albumin, glycated hemoglobin, and arterial stiffness in a general Chinese population

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ABSTRACT

*Background:* Both glycated albumin (GA) and glycated hemoglobin (HbA1c) reflect the mean glucose levels. This study was conducted to investigate the relationships among GA, HbA1c, and arterial stiffness in the general population.
*Methods:* A total of 11,014 participants were included. Serum GA; HbA1c; and arterial stiffness indices, including brachial-ankle pulse wave velocity (baPWV) and central systolic blood pressure (cSBP), were measured. Single-factor and multivariate regression analyses were performed. Receiver operating characteristic (ROC) analysis was performed to compare the predictive value of GA, HbA1c, and their combination for arterial stiffness. All analyses were stratified by sex.
*Results:* Men had a lower GA level than women. GA, HbA1c, and plasma glucose levels were correlated. The levels of baPWV and cSBP increased across sex-specific quartiles of GA and HbA1c ($P$ for trend < 0.001 for all). Both GA and HbA1c were positively related to elevated baPWV and cSBP after adjusting for conventional factors ($P < 0.05$ for all). These relationships remained significant when participants were divided into groups with normal glucose tolerance, prediabetes, or diabetes. Regarding screening for elevated baPWV and cSBP, the values of the area under the ROC curve (AUC) for GA were similar to those for HbA1c in men but were lower than those for HbA1c in women. The combination of GA and HbA1c did not improve the AUC compared with HbA1c alone.
*Conclusions:* Both GA and HbA1c were associated with arterial stiffness. The predictive value of GA for arterial stiffness was similar in men but lower in women compared with that of HbA1c.


## 1. Introduction

Arterial stiffness is a major cause of cardiovascular disease (CVD) [1]. Previous studies have reported that deteriorating glucose tolerance was associated with a decrease in systemic arterial compliance and distensibility and a generalized increase in central and peripheral arterial stiffness [2,3]. Recently, associations between glycemic markers, such as plasma glucose, glycated hemoglobin (HbA1c), and glycated albumin (GA), and arterial stiffness have been demonstrated in patients with diabetes or chronic kidney disease [3–5]. HbA1c was also associated with arterial stiffness in the general population [6].

HbA1c reflects the mean glucose levels over the previous 2–3 months, while GA reflects the mean glucose levels over the previous 2–3 weeks [7,8]. Previous reports have demonstrated the advantages of GA over HbA1c in reflecting glycemic excursion and postprandial glucose levels [9–11]. Postprandial hyperglycemia and plasma glucose fluctuations are known to have a greater impact on the development of vascular damage than the mean glucose levels are [12,13]. Thus, GA may be more closely associated with arterial stiffness than HbA1c is. Previous studies have shown that GA was superior to HbA1c in

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evaluating diabetic nephropathy and coronary artery disease [14–17]. However, other reports have indicated that GA and HbA1c were similarly associated with coronary heart disease and cardiovascular mortality [18]. To date, limited data are available on the association of GA with arterial stiffness in the general population, and no studies have compared GA and HbA1c for screening for arterial stiffness.

## 2. Methods

### 2.1. Study population

The participants recruited for this study had been admitted to the Chinese PLA General Hospital (Beijing, China) and had undergone a routine physical examination between January 2012 and June 2014. Subjects were included if they were >18 y. Individuals with anemia, liver cirrhosis or liver cancer, chronic kidney disease with an estimated glomerular filtration rate (GFR) < 60 ml/min/1.73 $m^2$, active thyroid disorders, or pregnancy were excluded. A total of 11,210 individuals were invited to complete standardized questionnaires, a 75-g oral glucose tolerance test (OGTT), serum GA and HbA1c measurements, and assessments of arterial stiffness. After 196 individuals with incomplete demographic information or physical examinations were further excluded, 11,014 participants were ultimately included in the study. The study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital. Written informed consent was obtained from all participants.

### 2.2. Data collection

Information on demographic characteristics, smoking status, alcohol consumption, medication use, and individual and family medical histories was obtained via a standard questionnaire, as described elsewhere [19,20]. Current smoking was defined as smoking at least one cigarette per day. Alcohol consumption was stratified into no alcohol, <20 g/day, 20–39 g/day, and ≥40 g/day. A history of CVD was defined as any prior stroke or coronary heart disease. Weight and height were measured, and body mass index was calculated. Seated systolic and diastolic blood pressures were measured twice in the right arm after 10 min of rest with a mercury sphygmomanometer, and the means of the 2 measurements were used for analysis. The mean arterial pressure was calculated as (2 * diastolic pressure + systolic pressure) / 3.

### 2.3. Laboratory measurements

Blood samples were collected at 0 and 2 h after patients fasted overnight. The samples were collected in tubes containing separating gel and were then immediately centrifuged. Serum aliquots were frozen at −70 °C to −80 °C and thawed just before testing. Fasting and 2-h postprandial plasma glucose levels, triglycerides, low-density lipoprotein (LDL) cholesterol, albumin, and creatinine were measured by routine laboratory methods, as previously described [19]. The estimated GFR was calculated using the Modification of Diet in Renal Disease eq. [21]. Serum high-sensitivity C-reactive protein (hsCRP) was determined using an immunoturbidimetric assay (Siemens Healthcare Diagnostics). Serum HbA1c was measured using high-performance liquid chromatography (Bio-Rad Inc.) certified by the National Glycohemoglobin Standardization Program. Serum GA was determined using an enzymatic method via a Lucica GA-L kit (Asahi Kasei Pharma Co) on a Hitachi 7600 chemistry analyzer (Hitachi). This parameter is expressed as the percentage of total albumin and was calculated as [(glycated albumin in g/dl/serum albumin in g/dl) * 100 / 1.14] + 2.9. The coefficient of variation was 2.5% at 0.44 g/dl and 1.4% at 1.23 g/dl. All measurements were performed by trained personnel blinded to the data.

### 2.4. Measurements of cSBP and baPWV

cSBP and baPWV were measured in the supine position after a 10-min rest, as previously described [20]. Briefly, applanation tonometry of the radial artery with a high-fidelity transducer (Millar Instruments) was used to obtain an averaged radial pulse. The radial artery pressure waveform was calibrated to a supine brachial blood pressure. The in-built transfer function in the SphygmoCor system (Atcor) provided a corresponding aortic pulse waveform from which the cSBP was identified. The baPWV was calculated using a volume plethysmograph (PP1100, Hanbyul Meditech). All recordings were performed on the right side of the body. All measurements were performed in triplicate by trained investigators, and the mean values were used for analysis. The intra-day coefficients of variations were 5.8% and 4.9% for cSBP and baPWV, respectively.

### 2.5. Diagnosis of glucose tolerance status

Glucose levels during the OGTT were used as the diagnostic standard. Normal glucose tolerance was defined as fasting plasma glucose <6.1 mmol/l and 2-h postprandial plasma glucose <7.8 mmol/l [22]. Prediabetes was defined as either an impaired fasting glucose (fasting glucose ≥6.1 mmol/l and <7 mmol/l and 2-h glucose <7.8 mmol/l) and/or an impaired glucose tolerance (2-h glucose ≥7.8 mmol/l and <11.1 mmol/l and fasting glucose <7.0 mmol/l). Diabetes was defined as fasting glucose ≥7.0 mmol/l, 2-h glucose ≥11.1 mmol/l, and/or antidiabetic medication use.

### 2.6. Statistical analysis

All analyses were stratified by sex based on the difference in GA values between men and women in the study. Triglycerides and hsCRP were log-transformed to improve the skewed distribution before the analyses. Comparisons of variables between the groups were performed using a chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables, and the *P* for the trend was calculated. Partial correlation analysis of glycemic markers was performed. Then, the participants were divided into sex-specific quartiles based on their serum GA levels (the first, second, third, and fourth quartiles were respectively <12.1, 12.1–13.1, 13.1–14.4, and ≥14.4 in men and <12.8, 12.8–13.6, 13.6–14.5, and ≥14.5 in women) and HbA1c levels (the first, second, third, and fourth quartiles were respectively <5.3, 5.3–5.6, 5.6–6.0, and ≥6.0 in men and <5.3, 5.3–5.5, 5.5–5.8, and ≥5.8 in women). baPWV and cSBP were also divided into sex-specific quartiles, and the upper sex-specific quartiles of baPWV (≥14.69 m/s in men and 13.72 m/s in women) and cSBP (≥135 mm Hg in men and 126 mm Hg in women) were defined as indicating an elevation. The values of the arterial stiffness indices across the quartiles of GA and HbA1c were compared. Several multivariate logistic regression analyses were performed to assess associations among GA, HbA1c, and elevated arterial stiffness indices. GA and HbA1c were set as categorical variables in the models.

To explore alternative explanations for our findings, we divided the participants into groups with normal glucose tolerance, prediabetes, or diabetes according to glucose tolerance status. Associations among GA, HbA1c, and elevated arterial stiffness indices were reassessed in all groups using multivariate logistic regression models. GA and HbA1c were set as continuous variables in the models. Furthermore, the predictive value of GA, HbA1c, and their combination for elevated arterial stiffness indices was calculated by constructing receiver operating characteristic (ROC) curves, and comparisons of the ROC curves were performed using the Delong method. All analyses were performed using SPSS ver 18.0 and a 2-sided *P* value < 0.05 was considered to be statistically significant.