Postprint: Association of Glycated Albumin and Glycated Hemoglobin with Aortic Valve Calcification in Patients with Moderate-to-Severe Aortic Valve Disease

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Abstract

Background: Aortic valve calcification (AVC) is a common aortic valvular lesion and a frequent manifestation of cardiovascular disease. Glycated albumin and glycated hemoglobin are closely associated with the occurrence and development of cardiovascular disease, but their relationship with aortic valve calcification in patients with aortic valve disease remains unclear. Objective: To investigate the relationship between glycated albumin, glycated hemoglobin, and aortic valve calcification. Methods: A total of 237 patients with aortic valve disease hospitalized at the Second Affiliated Hospital of Soochow University and the Fourth Affiliated Hospital of Soochow University from January 2015 to January 2023 were retrospectively enrolled as study subjects. Based on CT evaluation results, patients were divided into an aortic valve calcification group (188 cases) and a non-calcification group (49 cases). General patient data and laboratory examination indicators including glycated albumin, glycated hemoglobin, and fasting blood glucose were collected. Differences in general data and laboratory examination indicators between the two groups were compared, and multivariate Logistic regression analysis was used to evaluate influencing factors of AVC. Receiver operating characteristic (ROC) curve was used to assess the value of glycated albumin and glycated hemoglobin in predicting AVC, and the area under the ROC curve (AUC) was calculated. Results: Patients in the aortic valve calcification group had higher levels of glycated albumin, glycated hemoglobin, and fasting blood glucose than those in the non-calcification group, with statistically significant differences ($P<0.05$). Multivariate Logistic regression analysis showed that age and fasting blood glucose were independent risk factors for AVC ($P<0.05$). ROC curve analysis revealed that the AUC value of glycated albumin for predicting AVC was 0.620 (95%CI=0.529~0.711), with an optimal cutoff

value of 15.85, sensitivity of 0.559, and specificity of 0.694. The AUC value of glycated hemoglobin for predicting AVC was 0.609 (95%CI=0.522~0.696), with an optimal cutoff value of 6.15, sensitivity of 0.431, and specificity of 0.796. Conclusion: Abnormal glycemic metabolism indicators such as glycated albumin, glycated hemoglobin, and fasting blood glucose are associated with AVC, and glucose metabolism disorder is an influencing factor of AVC.

Full Text

Association of Glycated Albumin and Glycated Hemoglobin with Aortic Valve Calcification in Moderate to Severe Valvular Heart Disease Patients

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Abstract

Background Aortic valve calcification (AVC) is a common aortic valve disease and a frequent manifestation of cardiovascular disease. Glycated albumin and glycated hemoglobin are closely associated with the occurrence and development of cardiovascular diseases, but their relationship with aortic valve calcification in patients with aortic valve disease remains unclear.

Objective To investigate the association of glycated albumin and glycated hemoglobin with aortic valve calcification.

Methods A retrospective study was conducted on 237 patients with moderate and severe aortic valve disease who were hospitalized at The Second Affiliated Hospital of Soochow University and The Fourth Affiliated Hospital of Soochow University between January 2015 and January 2023. Based on CT evaluation results, patients were divided into an aortic valve calcification group (188 cases) and a non-calcification group (49 cases). General patient information and laboratory indicators including glycated albumin, glycated hemoglobin, and fasting blood glucose were collected. Differences in general characteristics and laboratory indicators between the two groups were compared, and multivariate logistic regression analysis was used to evaluate influencing factors of AVC. Receiver operating characteristic (ROC) curves were used to assess the predictive value of glycated albumin and glycated hemoglobin for AVC, and the area under the ROC curve (AUC) was calculated.

Results Patients in the aortic valve calcification group had significantly higher levels of glycated albumin, glycated hemoglobin, and fasting blood glucose compared to the non-calcification group (P<0.05). Multivariate logistic regression analysis showed that age and fasting blood glucose were independent risk factors for AVC (P<0.05). ROC curve analysis revealed that the AUC value for glycated albumin in predicting AVC was 0.620 (95%CI=0.529~0.711), with an optimal cutoff value of 15.85, sensitivity of 0.559, and specificity of 0.694. The AUC value for glycated hemoglobin in predicting AVC was 0.609 (95%CI=0.522~0.696), with an optimal cutoff value of 6.15, sensitivity of 0.431, and specificity of 0.796.

Conclusions Abnormal glycemic metabolism indicators including glycated albumin, glycated hemoglobin, and fasting blood glucose are associated with AVC, suggesting that glucose metabolism disorder is an influencing factor of AVC.

Keywords Aortic valve calcification; Glycated albumin; Glycated hemoglobin; Blood glucose

Introduction

Aortic valve calcification (AVC) is a common manifestation of cardiovascular disease, typically associated with the progression of atherosclerosis and degenerative changes in heart valves. Its incidence increases significantly with age and can cause cardiac dysfunction and even heart failure when severe. Studies show that in 2019, there were 9.4 million patients with calcific aortic valve disease globally, with a trend of annual increase, seriously affecting human health [1-2]. Research has found that glycated albumin and glycated hemoglobin, as common biomarkers of diabetes and metabolic diseases, are closely related to the occurrence and development of cardiovascular diseases [3-4]. These two indicators reflect short-term blood glucose fluctuations and long-term glycemic control status, respectively. These glycation products can trigger inflammatory responses and oxidative stress reactions, affecting normal cardiovascular system function through multiple pathways [5-7]. Currently, no studies have reported on the relationship between glycated albumin and glycated hemoglobin and AVC. Given the irreversible nature and potential harm of AVC, early identification of high-risk patients is key to clinical early intervention and delaying or preventing AVC progression. This study evaluates the differences in glycated albumin and glycated hemoglobin in AVC patients and assesses their predictive value for AVC, aiming to provide reference for early identification and clinical intervention of AVC.

Methods

Study Subjects

We retrospectively enrolled 237 patients with aortic valve disease hospitalized at The Second Affiliated Hospital of Soochow University and The Fourth Affiliated

Hospital of Soochow University from January 2015 to January 2023, including 153 males and 84 females. Inclusion criteria: patients with moderate to severe aortic stenosis and/or moderate to severe aortic regurgitation confirmed by CT and echocardiography. Exclusion criteria: (1) congenital bicuspid valve; (2) malignant tumor; (3) severe hepatic insufficiency; (4) infectious or hemorrhagic diseases; (5) incomplete data. This study was approved by the Ethics Committees of both hospitals (JD-HG-2023-72, 2023 伦研批 231002), and all patients or their families signed informed consent forms.

Diagnostic Criteria and Grouping

All enrolled patients underwent thin-slice CT examination. The presence of aortic valve calcification was evaluated using CT double-oblique transverse reconstruction [8]. The calcification index served as the diagnostic standard for AVC, with four grades based on the calcification index value: grade 0 indicating no calcification, grades 1-99 indicating mild calcification, grades 100-399 indicating moderate calcification, and grade 400 or above indicating severe calcification. Coronary artery calcification was assessed using the Agatston method [9], identifying lesions with CT values $ $130 Hounsfield units (HU) in the coronary artery course as coronary calcification plaques.

Based on whether the calcification index was zero, patients were divided into two groups: a calcification group (188 cases with non-zero calcification index) and a non-calcification group (49 cases with calcification index of zero).

Data Collection

General patient information including gender, age, BMI, smoking history, hypertension history, and diabetes history was collected. Smoking history was defined as current or past active smoking habit. Hypertension history was defined as patients currently taking antihypertensive medication or with measured systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg during previous or hospital stays. Diabetes history was defined as patients currently taking hypoglycemic medication and/or using insulin to control blood glucose.

Laboratory test data were collected including glycated albumin, glycated hemoglobin, fasting blood glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen, serum creatinine, and uric acid. Glycated albumin and glycated hemoglobin were measured using the BIO-RAD D-100 high-performance liquid chromatography system, while other biochemical indicators were measured using the Roche Cobas c702 automatic biochemical analyzer.

Statistical Analysis

Data were analyzed using SPSS 23.0 software. Normally distributed measurement data were expressed as ($\bar{x}\pm s$) and compared between groups using independent samples t-test. Non-normally distributed data were expressed as M(P25,

P75) and compared using non-parametric tests. Count data were expressed as composition ratios and compared using ^{2} test. Univariate logistic regression analysis was used to evaluate the relationship between each variable and AVC. Variables with statistical significance were further included in multivariate logistic regression analysis to assess independent influencing factors of AVC. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive value of glycated albumin and glycated hemoglobin for AVC, and the area under the curve (AUC) was calculated. $P<0.05$ was considered statistically significant.

Results

Comparison of General Characteristics and Laboratory Indicators

Patients in the calcification group had significantly higher age, glycated albumin, glycated hemoglobin, fasting blood glucose, and coronary artery calcification rate compared to the non-calcification group ($P<0.05$). There were no significant differences between the two groups in gender, smoking history, hypertension history, diabetes history, BMI, serum albumin, triglycerides, total cholesterol, LDL-C, HDL-C, blood urea nitrogen, serum creatinine, or uric acid ($P>0.05$). See Table 1 .

Univariate Logistic Regression Analysis for AVC Influencing Factors

Using AVC as the dependent variable (assignment: present=1, absent=0) and gender (male=1, female=0), age (actual value), smoking history (present=1, absent=0), hypertension history (present=1, absent=0), diabetes history (present=1, absent=0), BMI (actual value), glycated albumin (actual value), glycated hemoglobin (actual value), albumin (actual value), fasting blood glucose (actual value), triglycerides (actual value), total cholesterol (actual value), LDL-C (actual value), HDL-C (actual value), blood urea nitrogen (actual value), serum creatinine (actual value), uric acid (actual value), and coronary artery calcification (present=1, absent=0) as independent variables, univariate logistic regression analysis showed that age (OR=1.063, 95%CI=1.023~1.104), glycated albumin (OR=1.145, 95%CI=1.010~1.298), glycated hemoglobin (OR=1.559, 95%CI=1.012~2.401), fasting blood glucose (OR=1.5, 95%CI=1.178~1.967), and coronary artery calcification (OR=2.529, 95%CI=1.307~4.895) were risk factors for AVC. See Table 2 .

Multivariate Logistic Regression Analysis for AVC Influencing Factors

Further multivariate logistic regression analysis showed that age (OR=1.060, 95%CI=1.019~1.103) and fasting blood glucose (OR=1.478, 95%CI=1.147~1.906) were independent risk factors for AVC. See Table 3 .

ROC Curve Analysis of Glycated Albumin and Glycated Hemoglobin for Predicting AVC

The ROC curve analysis showed that the AUC value for glycated albumin in predicting AVC was 0.620 (95%CI=0.529~0.711), with an optimal cutoff value of 15.85, sensitivity of 0.559, and specificity of 0.694. The AUC value for glycated hemoglobin in predicting AVC was 0.609 (95%CI=0.522~0.696), with an optimal cutoff value of 6.15, sensitivity of 0.431, and specificity of 0.796. See Figure 1 [Figure 1: see original paper].

Discussion

AVC is an important factor affecting cardiac valve function, characterized by thickening, fibrosis, and calcification of aortic valve leaflets. With the aging of society and the increasing population of patients with chronic diseases such as hypertension and diabetes, the incidence of AVC has increased sevenfold, and complications such as heart failure, arrhythmia, and cerebral embolism have imposed an increasingly heavy social burden [10-11]. Exploring factors related to the occurrence and development of AVC is of great significance for effectively preventing AVC progression and reducing the incidence of aortic valve disease. This study found that AVC patients had higher age, glycated albumin, glycated hemoglobin, and fasting blood glucose levels than the non-calcification group, and that fasting blood glucose and age were independent risk factors for AVC. Both glycated albumin and glycated hemoglobin showed moderate predictive value for AVC occurrence.

Metabolic factors and related diseases are associated with heart valve calcification. A Swedish study showed that male sex, age, diabetes, hypertension, obesity, smoking, and elevated plasma lipoprotein(a) and LDL-C levels were positively correlated with increased risk of calcific aortic valve disease [12-13]. A study from Beijing Fuwai Hospital found that elevated blood glucose could accelerate the progression of valvular diseases including calcific aortic valve disease [14]. YANG et al. [15] reported that hemoglobin glycation index was positively associated with increased risk of cardiovascular disease-related mortality. Other studies have found that changes in glycated hemoglobin levels are associated with coronary artery calcification disease, and follow-up results showed that progressive elevation of glycated hemoglobin levels increased the risk of coronary artery calcification, particularly in patients with concurrent hyperglycemia [16-17]. Glycated albumin is associated with coronary atherosclerotic heart disease and can serve as a supplementary indicator to glycated hemoglobin in special conditions such as hemoglobinopathy, pregnancy, or chronic kidney disease [18], but its relationship with AVC has not been reported. Our results suggest that both glycated hemoglobin and glycated albumin are associated with AVC, and elevated levels are risk factors but not independent risk factors for AVC, which is consistent with BEBU et al.' s [4] research on the relationship between glycated hemoglobin and cardiovascular disease risk. The reason may be that elevated glycated hemoglobin levels are partially mediated by blood glu-

cose levels or non-glycemic factors, thus preventing glycated hemoglobin from being an independent risk factor for cardiovascular disease.

Oxidative stress and inflammatory response are key pathophysiological mechanisms in the development of AVC [19]. As indicators of long-term and short-term glycemic control, glycated hemoglobin and glycated albumin may participate in the occurrence and development of AVC by promoting oxidative stress and inflammatory responses. On one hand, elevated glycated albumin and glycated hemoglobin reflect the accumulation of advanced glycation end products (AGEs). AGEs regulate multiple cellular processes by binding to the receptor for advanced glycation end products (RAGE), generating excessive inflammatory factors and promoting the calcification process [20-21]. On the other hand, hyperglycemia-induced oxidative stress not only directly damages vascular endothelial cells and valvular interstitial cells, but also increases the production of oxygen free radicals and activates more pro-calcification signaling pathways, such as bone morphogenetic proteins, further promoting AVC progression [22-23]. Additionally, hyperglycemia-induced mitochondrial dysfunction promotes the production of large amounts of reactive oxygen species and the uncoupling of nitric oxide synthase isoforms from endothelial cells, thereby causing damage to valvular endothelial cells and promoting the development of valvular disease [24-25].

In this study, age and fasting blood glucose were independent risk factors for AVC. The association between age and AVC may stem from valvular endothelial dysfunction and chronic inflammation, which together promote the transformation of valvular interstitial cells into an osteogenic phenotype. Furthermore, this study found no correlation between hypertension, blood lipid indicators, or BMI and AVC, which differs from the results of LARSSON et al. [12]. This discrepancy may be related to sample size and control group selection, as their sample comprised patients undergoing aortic and mitral valve surgery with more severe valvular disease and larger sample size. Additionally, it may be related to dietary structure differences among populations in different countries and regions [26]. Nordic populations tend to use protein and lipids as primary daily energy sources [27], while Asian populations prefer grains and starches as main energy sources. Therefore, we speculate that hyperlipidemia directly caused by dietary intake may be more likely to lead to valvular disease than that caused by increased biological transformation and synthesis.

Our ROC curve analysis showed that the AUC value for glycated albumin in predicting AVC (0.620) was slightly higher than that for glycated hemoglobin (0.609), but both were at a moderate predictive level with low sensitivity, potentially missing some diagnoses. The predictive ability of glycated albumin and glycated hemoglobin for AVC is limited, but they still have certain clinical reference value as auxiliary indicators. Future studies could combine other biomarkers or imaging indicators to construct multifactorial prediction models to improve diagnostic accuracy and further validate the universality of cutoff values in different populations.

This study has several limitations: (1) The overall sample size was relatively small, affecting the judgment of some results. For example, diabetes is a common risk factor for calcific aortic valve disease, and the prevalence of diabetes in the calcification group was higher than in the non-calcification group, but the difference was not statistically significant, possibly due to the small sample size. (2) This was a retrospective cross-sectional study, and information on medication use, long-term disease course, and follow-up results were not obtained, affecting the assessment of glycated albumin and glycated hemoglobin indicators on AVC progression and long-term prognosis.

In conclusion, abnormal glycemic metabolism indicators including glycated albumin, glycated hemoglobin, and fasting blood glucose are associated with AVC, suggesting that glucose metabolism disorder is an influencing factor of AVC, which has certain guiding significance for the prevention and treatment of calcific aortic valve disease. Meanwhile, controlling metabolic abnormalities and metabolic diseases is of great importance for the prevention and treatment of heart valve diseases.

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Note: Figure translations are in progress. See original paper for figures.