

Elevated Glycated Albumin in Serum Is Associated with Adverse Cardiac Outcomes in Patients with Acute Coronary Syndrome Who Underwent Revascularization Therapy

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Aims: The associations between increased glycated albumin (GA) in the serum and diabetic complications and mortality have been revealed in the general population. However, less is known regarding the prognostic value of GA in patients diagnosed with acute coronary syndrome (ACS).

Methods: In this study, all patients admitted for ACS who underwent a successful percutaneous coronary intervention (PCI) at our center from January 2018 to February 2019 were retrospectively examined. Clinical characteristics, laboratory results (e.g., serum GA levels), and procedural details were collected. The primary outcome included a composite of major adverse cardio-cerebral events (MACCE), such as death, myocardial infarction, stroke, and unplanned revascularization. The association between serum GA levels and clinical outcomes was tested in three multivariable models using Cox proportional hazard analysis. Subgroup analysis was performed in patients who were diagnosed with diabetes versus patients without diabetes.

Results: A total of 1,806 ACS patients (mean age of 59.4 years; 77.8% were men; 44.9% were diagnosed with diabetes) were enrolled in this study, where the majority exhibited unstable angina (81.6%) and showed preserved left ventricular systolic function. Patients in the high GA level group were commonly female and were more likely to have metabolic disorders and to exhibit severe CAD (all $p < 0.05$). MACCE occurred in 126 patients (7.0%) during a mean follow-up time of 17.2 months. The cumulative risk of MACCE at the 18-month follow-up visit significantly increased in a stepwise fashion along with increased GA levels (log-rank $p = 0.018$) in the serum. The association between serum GA levels and MACCE was further determined after adjusting traditional risk factors and hemoglobin A1c (HbA1c) (GA, per 1% increase: hazard ratio [HR] 1.09, 95% confidence interval [CI] 1.06–1.13; GA, higher vs. lower tertial: HR 1.92, 95% CI 1.01–3.67). In a subgroup analysis, the prognostic role of serum GA only existed in diabetic patients, even when adjusting for traditional risk factors and HbA1c levels.

Conclusions: Elevated GA levels in the serum were associated with poor intermediate-term outcomes in low-risk ACS patients who underwent PCI, especially in patients with preexisting diabetes.

Key words: Glycated albumin, Acute coronary syndrome, Percutaneous coronary intervention, Outcomes, Diabetes

Introduction

Type 2 diabetes mellitus is a risk factor for the

occurrence and development of coronary artery disease (CAD). In diabetic patients, increased fasting glucose levels and poor long-term glycemic control (e.g.,

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elevated hemoglobin A1c [HbA1c]) are associated with worse cardiovascular outcomes^{1, 2}. Even mild disturbances in glucose metabolism contribute to CAD^{3, 4}. HbA1c has been used in clinical practice for the diagnosis and monitoring of diabetes. However, HbA1c is unable to show short-term glycemic variability when glucose-lowering therapies are initiated or adjusted. Meanwhile, the accuracy of interpreting HbA1c is affected by hemoglobin uptake rate, medications, race, and certain diseases (e.g., hemodialysis)⁵.

Given these limitations, there has been growing interest in determining new hyperglycemic markers as adjuncts or alternatives⁶. Out of these novel potential markers, glycated albumin (GA) has been shown to perfectly correlate with HbA1c and has also shown to be excellent in overcoming the disadvantages observed when using HbA1c⁷. Importantly, the predictive value of GA for diabetic complications and mortality has been identified for both general and diabetic populations. In a large community-based population ($n=12,306$) study, serum GA levels were found to be significantly associated with the incidence of diabetes, diabetic microvascular complications, vascular outcomes, and mortality during a two-decade follow-up^{8, 9}. Recently, a meta-analysis that included dialysis patients diagnosed with diabetes showed that increased GA was a predictor of all-cause mortality (hazard ratio [HR] 1.02, 95% confidence interval [CI] 1.01–1.03), but not cardiac mortality (HR 1.03, 95% CI 0.99–1.06)¹⁰. However, the prognostic value of GA was only minimally examined in CAD patients, particularly patients diagnosed with acute coronary syndrome (ACS), a severe manifestation of CAD. Given the close relationship between glucose metabolism disorders and CAD, we performed a study to investigate the predictive value of serum GA for intermediate-term outcomes in a large number of diabetic and non-diabetic hospitalized patients who underwent successful PCI for ACS.

Aim

To investigate the predictive value of serum GA for intermediate-term outcomes in a large number of diabetic and non-diabetic hospitalized patients that underwent successful PCI for ACS.

Methods

Study Population

Patients who were admitted for ACS and who subsequently underwent successful PCI from January 2018 to February 2019 at Beijing Anzhen Hospital,

Capital Medical University were retrospectively reviewed. The main patient exclusion criteria are as follows: (1) age <18 years; (2) presentation of stable angina; (3) not suitable for PCI treatment or unsuccessful procedures; (4) acute decompensated heart failure or cardiogenic shock; (5) severe dysfunction in the liver, kidney, or thyroid that could affect the interpretation of GA results; and (6) lack of baseline data or follow-up time <1 month. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University.

Procedures

Diagnostic coronary angiography, PCI, and periprocedural management were performed following current guidelines. Coronary angiography was performed using a 5 F or 6 F (1 F=0.33 mm) catheter with transradial or transfemoral access. CAD was defined as the presence of at least one lesion with a luminal diameter stenosis $\geq 50\%$ in any major epicardial coronary artery. The decision for PCI was based on the discretion of the operator. All coronary stents were second-generation drug-eluting stents. Generally, patients received dual antiplatelet therapy (e.g., aspirin and clopidogrel) for 12 months after receiving a stent and then received lifelong aspirin monotherapy.

Data Collection

Clinical characteristics, echocardiographic findings, laboratory results, and procedural details were collected by trained physicians using a dedicated case report form. Diabetes was defined as fasting glucose levels ≥ 7.0 mmol/L or a prior diagnosis of diabetes or current administration of hypoglycemic treatment. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Biochemical indexes (e.g., GA) were measured using serum samples at the central laboratory of our hospital prior to the PCI procedure. Generally, blood samples from all patients were collected in the morning after patients fasted for 12 h overnight.

Clinical Outcomes

The primary outcome in this study included a composite of major adverse cardio-cerebral events (MACCE), such as death, myocardial infarction (MI), stroke, and unplanned revascularization, while secondary outcomes included death, MI, stroke, and unplanned revascularization. MI was defined as an elevation in cardiac troponin levels above the 99th percentile upper reference limit accompanied by ischemia symptoms, new ischemic electrocardiography

changes, development of pathologic Q waves, or new imaging evidence consistent with ischemic etiology. Procedure-related MI (type 4 or 5) was not considered an adverse outcome¹¹). Stroke was diagnosed by a neurologist based on the presence of neurologic deficits and imaging studies. Unplanned revascularization referred to a percutaneous or surgical coronary revascularization procedure that was not planned during hospitalization. Patients were routinely followed up every 3 months after being discharged from the hospital by telephone, through office interviews, or by reviewing medical records.

Statistical Analysis

Since there were no established cut-points for GA, we divided patients (main analysis) or patient subsets with or without diabetes (subgroup analysis) into three groups based on serum GA levels. Continuous variables were expressed as mean \pm standard deviation. Mean (or median) values were compared using one-way analysis of variance or the Kruskal–Wallis H test when appropriate. Categorical variables were expressed as percentages and analyzed using the Chi-square test or Fisher's exact test. Cumulative risk of clinical outcomes was assessed using Kaplan–Meier estimates. Statistical significance was evaluated using the log-rank test. The association between serum GA levels (modulated as continuous or categorical variables) and clinical outcomes was examined in four multivariable models using Cox proportional hazard analysis. Variables in each model showed a $p < 0.1$ in univariate analysis or were clinically relevant to the outcomes. Model 1 consisted of demographics (age, sex, and BMI). Model 2 included cardiac comorbidities, medical history, the extent of CAD on angiograms, and demographics (age, sex, BMI, smoking status, hypertension, hyperlipidemia, eGFR < 90 ml/min/1.73 m², prior MI, stroke, prior coronary intervention, prior coronary bypass surgery, SYNTAX score, multi-vessel disease, and long lesion). Model 3 was a comprehensive model containing variables in model 2 and HbA1c. The receiver operating characteristic curve and the Youden Index were used to further identify the optimal cutoff value for serum GA levels in predicting clinical outcomes with maximum potential effectiveness. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 22.0 software (IBM, Armonk, New York).

Results

Patient Characteristics

A total of 1,806 ACS patients who underwent successful PCI (mean age was 59.4 years; 77.8% were men) were enrolled in this study. In this group, 811 patients (44.9%) were diagnosed with diabetes, with average GA levels being 16.8%. Most of the patients presented unstable angina (81.6%) with preserved left ventricular systolic function (mean ejection fraction, 61.1%) (Table 1). Multi-vessel coronary stenosis was common (56.6%) and nearly half of the patients underwent PCI for left anterior descending artery stenosis (Table 2).

Based on serum GA levels, the entire study population was divided into three groups: the lower GA group (9.2%–14.4%), median GA group (14.4%–17.1%), and higher GA group (17.1%–46.9%). Patients with increased GA levels in the serum were more likely to be female; have higher systolic blood pressure, higher triglyceride levels, and total cholesterol levels, and have been diagnosed with diabetes (all $p < 0.05$, Table 1). Meanwhile, the extent of CAD was more severe (e.g., multi-vessel stenosis) in patients in the higher GA group ($p < 0.05$, Table 2).

Clinical Outcomes

All patients had a clinical follow-up > 1 month, with a mean follow-up time being 17.2 months. MACCE, composed of death, MI, stroke, and unplanned revascularization, occurred in 126 patients (7.0%), predominately driven by unplanned revascularization (5.0%), while the incidence of death (0.8%), MI (1.3%), or stroke (0.5%) was generally low (Table 3).

Fig. 1A shows that the cumulative risk of MACCE at the 18-month follow-up significantly increased in a stepwise fashion with increased serum GA levels (from lower to higher GA levels) (log-rank $p = 0.018$). This time-to-risk pattern was not observed in patients without diabetes (log-rank $p = 0.777$, Fig. 1B) but persisted in diabetic patients (log-rank $p < 0.001$, Fig. 1C).

Multivariate Analysis

When GA was modulated as a continuous variable, GA levels (per 1% increase) were significantly associated with the occurrence of MACCE based on univariate analysis. This association was further demonstrated in multiple multivariate models adjusting for demographics (model 1), demographics, cardiac comorbidities, medical histories, and the extent of CAD (model 2) and model 3 (consisting of variables in model 2 plus HbA1c). Moreover, the

Table 1. Baseline characteristics according to glycated albumin levels

	Overall N=1806	Tertiles of glycated albumin levels			P value
		Lower (9.2%-14.4%) n=637	Median (14.4%-17.1%) n=581	Higher (17.1%-46.9%) n=588	
Demographics					
Age, years	59.4 ± 10.0	55.7 ± 10.2	61.7 ± 9.2	61.0 ± 9.6	<0.001
Male, %	1405 (77.8)	528 (82.9)	445 (76.6)	432 (73.5)	<0.001
BMI, kg/m ²	26.0 ± 3.2	26.3 ± 3.3	25.7 ± 3.4	26.0 ± 3.0	0.004
Heart rate, bpm	70.5 ± 14.8	70.1 ± 14.7	69.8 ± 14.6	71.6 ± 15.2	0.078
SBP, mmHg	126.8 ± 23.5	124.5 ± 25.7	127.6 ± 20.1	128.5 ± 23.9	0.007
Clinical presentations, %					
Unstable angina	1473 (81.6)	508 (79.7)	480 (82.6)	485 (82.5)	0.341
NSTEMI	163 (9.0)	60 (9.4)	48 (8.3)	55 (9.4)	0.737
STEMI	170 (9.4)	69 (10.8)	53 (9.1)	48 (8.2)	0.267
Medical histories, %					
Current smoking	668 (37.0)	260 (40.8)	198 (34.1)	210 (35.7)	0.038
Hypertension	1166 (64.6)	393 (61.7)	372 (64.0)	401 (68.2)	0.056
Diabetes	811 (44.9)	53 (8.3)	206 (35.5)	552 (93.9)	<0.001
Hyperlipidemia	1278 (70.8)	465 (73.0)	411 (70.7)	402 (68.4)	0.205
Stroke	86 (4.8)	25 (3.9)	26 (4.5)	35 (6.0)	0.231
Prior myocardial infarction	263 (14.6)	89 (14.0)	82 (14.1)	92 (15.6)	0.661
Prior coronary intervention	585 (32.4)	206 (32.3)	183 (31.5)	196 (33.3)	0.798
Prior coronary bypass surgery	46 (2.5)	11 (1.7)	22 (3.8)	13 (2.2)	0.061
Echocardiographic findings					
Left ventricular ejection fraction, %	61.1 ± 8.2	61.7 ± 7.8	61.0 ± 8.3	60.5 ± 8.4	0.085
Laboratory tests					
Fasting glucose, mmol/L	7.1 ± 2.7	5.6 ± 0.9	6.4 ± 1.5	9.4 ± 3.3	<0.001
Glycated hemoglobin, %	6.6 ± 1.4	5.7 ± 0.5	6.2 ± 0.6	8.0 ± 1.4	<0.001
Glycated albumin, %	16.8 ± 4.4	13.3 ± 0.8	15.6 ± 0.8	21.8 ± 4.3	<0.001
Serum creatinine, μmol/L	77.2 ± 43.4	74.7 ± 38.9	76.8 ± 31.7	80.3 ± 55.9	0.079
eGFR, ml/min/1.73m ²	124.8 ± 46.6	131.8 ± 66.4	121.4 ± 28.2	120.5 ± 32.2	<0.001
Triglycerides, mmol/L	1.8 ± 1.5	1.9 ± 1.5	1.7 ± 1.4	2.0 ± 1.5	0.003
Total cholesterol, mmol/L	4.1 ± 1.1	4.1 ± 1.1	4.0 ± 1.0	4.1 ± 1.1	0.012
HDL-C, mmol/L	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.3	1.0 ± 0.3	0.003
LDL-C, mmol/L	2.4 ± 0.9	2.4 ± 0.9	2.3 ± 0.8	2.4 ± 0.8	0.026
Medications at discharge, %					
Any hypoglycemic agents	670 (37.1)	31 (4.9)	130 (22.4)	509 (86.6)	<0.001
Metformin	155 (8.6)	8 (1.3)	36 (6.2)	111 (18.9)	<0.001
Sulfonylureas	95 (5.3)	1 (0.2)	23 (4.0)	71 (12.1)	<0.001
α-glucosidase inhibitor	334 (18.5)	16 (2.5)	76 (13.1)	242 (41.2)	<0.001
Insulin	353 (19.5)	9 (1.4)	47 (8.1)	297 (50.5)	<0.001
Aspirin	1777 (98.4)	630 (98.9)	567 (97.6)	580 (98.6)	0.162
Clopidogrel	1296 (71.8)	440 (69.1)	417 (71.8)	439 (74.7)	0.095
ACEI or ARB	800 (44.3)	264 (41.4)	241 (41.5)	295 (50.2)	0.002
β-blocker	1186 (65.7)	417 (65.5)	367 (63.2)	402 (68.4)	0.172
Statins	1775 (98.3)	625 (98.1)	572 (98.5)	578 (98.3)	0.903

Data are reported as mean ± standard deviation or no. (%). BMI, body mass index; SBP, systolic blood pressure; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Coronary angiography and intervention according to glycated albumin levels

	Overall N=1806	Tertiles of glycated albumin levels			P value
		Lower (9.2%-14.4%) n=637	Median (14.4%-17.1%) n=581	Higher (17.1%-46.9%) n=588	
Angiography					
Left main artery lesion, %	406 (22.5)	149 (23.4)	136 (23.4)	121 (20.6)	0.404
Multi-vessel lesion, %	1022 (56.6)	320 (50.2)	303 (52.2)	399 (67.9)	<0.001
Chronic total occlusion lesion, %	412 (22.8)	139 (21.8)	140 (24.1)	133 (22.6)	0.634
Long lesion (>20 mm), %	763 (42.2)	186 (29.2)	194 (33.4)	383 (65.1)	<0.001
SYNTAX score	13.1 ± 7.3	12.6 ± 7.3	13.2 ± 7.4	13.5 ± 7.1	0.111
Intervention					
Left main artery lesion, %	215 (11.9)	81 (12.7)	71 (12.2)	63 (10.7)	0.535
Left anterior descending artery lesion, %	915 (50.7)	328 (51.5)	298 (51.3)	289 (49.1)	0.669
Left circumflex artery lesion, %	502 (27.8)	176 (27.6)	159 (27.4)	167 (28.4)	0.919
Right coronary artery lesion, %	626 (34.7)	214 (33.6)	203 (34.9)	209 (35.5)	0.763
Number of stents, /patient	1.7 ± 0.8	1.7 ± 0.8	1.7 ± 0.8	1.7 ± 0.8	0.075
Length of stents, mm/patient	38.2 ± 23.9	37.2 ± 23.0	39.8 ± 27.4	37.7 ± 21.1	0.242

Data are reported as mean ± standard deviation or no. (%).

Table 3. Clinical outcomes according to glycated albumin levels

	Overall N=1806	Tertiles of glycated albumin levels		
		Lower (9.2%-14.4%) n=637	Median (14.4%-17.1%) n=581	Higher (17.1%-46.9%) n=588
Primary outcome				
Composite of death, MI, stroke and unplanned revascularization	126 (7.0)	25 (3.9)	32 (5.5)	69 (11.7)
Secondary outcomes				
Death	15 (0.8)	4 (0.6)	5 (0.9)	6 (1.0)
MI	24 (1.3)	5 (0.8)	11 (1.9)	8 (1.4)
Stroke	9 (0.5)	3 (0.5)	3 (0.5)	3 (0.5)
Unplanned revascularization	91 (5.0)	18 (2.8)	19 (3.3)	54 (9.2)

Data are reported as no. (%). MI, myocardial infarction.

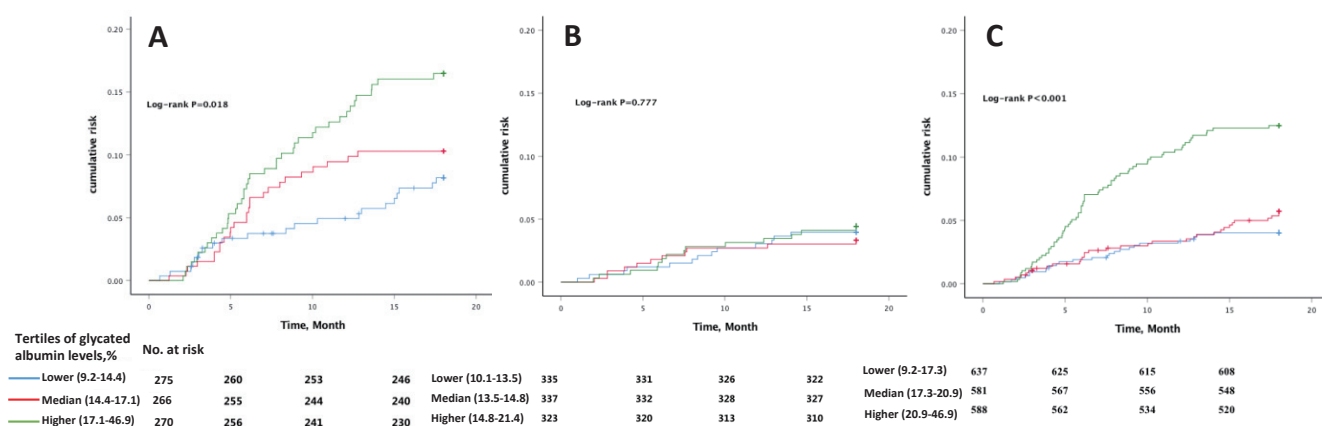


Fig. 1. Cumulative risk of the primary endpoint in the entire population (A), patients without diabetes (B), and patients with diabetes (C) according to tertiles of glycated albumin levels

Table 4. Association of glycosylated albumin levels with adverse cardiac events in Cox multivariate regression models

	Univariate analysis	Multivariate analysis		
		Model 1*	Model 2†	Model 3§
Entire Population				
Glycated albumin, per 1% increase	1.09 (1.06-1.12)	1.10 (1.06-1.13)	1.09 (1.05-1.12)	1.09 (1.06-1.13)
Tertiles of glycosylated albumin levels, %				
Lower (9.2-14.4)	Reference	Reference	Reference	Reference
Median (14.4-17.1)	1.40 (0.83-2.37)	1.33 (0.77-2.31)	1.33 (0.77-2.30)	1.21 (0.69-2.15)
Higher (17.1-46.9)	3.05 (1.93-4.82)	3.00 (1.86-4.85)	2.98 (1.85-4.82)	1.92 (1.01-3.67)
Diabetic subgroup				
Glycated albumin, per 1% increase	1.05 (1.01-1.10)	1.06 (1.02-1.11)	1.06 (1.02-1.10)	1.06 (1.02-1.10)
Tertiles of glycosylated albumin levels, %				
Lower (9.2-17.3)	Reference	Reference	Reference	Reference
Median (17.3-20.9)	1.27 (0.72-2.26)	1.50 (0.81-2.78)	1.53 (0.83-2.84)	1.53 (0.83-2.84)
Higher (20.9-46.9)	2.02 (1.20-3.41)	2.16 (1.21-3.86)	2.09 (1.17-3.73)	2.09 (1.17-3.73)

Data are reported as hazard ratio (95% confidence interval). *Model 1, adjusting for age, sex and body mass index; †Model 2, adjusting for variables in model 1, current smoking, hypertension, hyperlipidemia, eGFR <90 ml/min/1.73m², prior myocardial infarction, stroke, prior coronary intervention, prior coronary bypass surgery, SYNTAX score, multi-vessel disease and long lesion; §Model 3, adjusting for variables in model 2 and HbA1c.

independent prognostic value of GA persisted in the three multivariate models when GA was modulated as a categorical variable (Table 4). In particular, this was observed in patients showing obviously elevated GA levels (e.g., GA >15.9% [additional file: Supplemental Fig. 1]).

Importantly, the prediction of GA (modulated as a continuous or categorical variable) was demonstrated only in a subset of diabetic patients but not in non-diabetic patients, as shown by the comprehensive multivariate model 3 (Table 4). Diabetic patients with a GA >19.5% were at an increased risk for adverse outcomes (additional file: Supplemental Fig. 2). Notably, the prognostic value of GA, modulated as a continuous or categorized variable, was independent of HbA1c in either the entire population or the diabetic patients (Table 4).

Discussion

To the best of our knowledge, this is the first study to demonstrate that increased serum GA levels are independently associated with poor intermediate-term outcomes in a large number of low-risk ACS patients who underwent PCI. The following are the main findings of this study: (1) compared to the lower and median GA level groups, patients in the higher GA group were commonly female and were more likely to have metabolic disorders and more severe CAD, thus showing an increased risk of adverse outcomes; (2) in a comprehensive multivariable model, each 1% increment in GA levels was associated

with a 9% increased risk of adverse outcomes (moreover, markedly elevated GA levels (e.g., >17.1%, in the higher tertial) were associated with a ~2-fold risk of adverse outcomes); and (3) the prognostic value of GA, either modulated as continuous or categorical variables, was demonstrated only in diabetic patients, even after adjusting for co-variables and HbA1c levels but not in non-diabetic patients.

GA, a main Amadori-modified early glycation product, reflects glycemic control over the past 14 to 21 days. In addition to being a glycemic control index, GA is also involved in inflammatory diseases, particularly in diabetes-related diseases, including CAD¹². In the Hisayama Study that included 2,702 Japanese community dwellers, Naoko *et al.* found that increased serum GA levels were significantly associated with elevated carotid intima-media thickness (a sign of early atherosclerosis)¹³. A series of studies further showed that elevated serum GA levels positively correlated with the presence and severity of CAD in diabetic patients. In addition, this study showed that GA levels were correlated with CAD as opposed to HbA1c levels that were not as strongly correlated with CAD^{14, 15}. In line with these findings, ACS patients (~45% diabetes) with increased serum GA levels contained more prevalent cardiovascular risk factors and extensive CAD. More recently, Akane *et al.* reported 10-year follow-up results of the Hisayama Study showing that the highest quartile of serum GA levels (≥15.7%) was associated with a 2.2-fold increased incidence of CAD and a 2.5-fold higher risk

of stroke. Importantly, this association between higher serum GA levels and CAD development was independent of preexisting diabetes¹⁶. Collectively, increased serum GA levels positively correlated with the incidence, presence, and severity of CAD. Studies investigating outcomes of CAD patients with different serum GA levels are still needed.

Diabetic patients are more likely to show an early occurrence and accelerated CAD and exhibit less favorable outcomes despite revascularization therapy^{17, 18}. Yang *et al.* demonstrated that serum GA levels were an independent predictor of cardiac death, MI, and stroke in 576 stable CAD patients diagnosed with diabetes (HR 1.22, 95% CI 1.16–1.28) during a 2-year follow-up post-PCI¹⁹. To extend these findings, 1,806 ACS patients with or without diabetes were enrolled in this study to demonstrate that high GA serum levels were associated with a significantly increased risk of death, MI, stroke, and unplanned revascularization during an 18-month follow-up after successful PCI. This association was further tested by modulating GA as a continuous or categorized variable and determining a comprehensive multivariate model (GA, per 1% increase: HR 1.09, 95% CI 1.06–1.13; GA, higher vs. lower tertial: HR 1.92, 95% CI 1.01–3.67). Interestingly, in a subgroup analysis for patients with or without diabetes, we demonstrated that the prognostic role of serum GA only existed in diabetic patients, even when adjusting for traditional risk factors and HbA1c levels.

Most of the patients in our study were relatively young (mean age of 59 years), presented unstable angina (~82%), preserved ejection fraction (mean value of 61%), and showed less complex coronary stenosis (mean SYNTAX score of 13). These characteristics indicated a low-risk profile of the ACS population, which resulted in a generally low incidence of MACCE, particularly less occurrence of “hard” endpoints (e.g., death, MI, or stroke) during intermediate-term follow-ups. Therefore, the observed prognostic role of GA in this study was predominately driven by unplanned revascularization in diabetic patients. Consistent with our findings, several studies investigating Chinese diabetic patients showed that higher serum GA levels were associated with in-stent restenosis (ISR), negative coronary artery remodeling, and impaired coronary collateralization^{20–22}.

Notably, in this study, the prognostic value of GA and HbA1c was different—GA was able to predict MACCE independent of traditional risk factors and HbA1c, whereas HbA1c was unable to predict MACCE when adjusting for GA (HR 1.17, 95% CI 0.92–1.12). To explain the prognostic superiority of GA to HbA1c, one reason may be that GA is a better

indicator for glucose fluctuation and excursion (e.g., poor glycemic control) prior to ACS onset than HbA1c^{23, 24}. Large glucose excursion has been shown to enhance oxidative stress and accelerate atherosclerosis^{25, 26}. These hypotheses were further supported by our previous publication and a recent meta-analysis demonstrating that greater glucose excursion is an independent predictor of MACE in patients with CAD who underwent PCI during a short-term and an intermediate-term follow-up^{27, 28}. Another reason could be that high GA, while not HbA1c, is an independent predictor of low response to clopidogrel in ACS patients^{29–31}, which is associated with higher risk of ISR, stent thrombosis, and recurrent of MI. Collectively, the prognostic value of GA superior to HbA1c remains unclear; therefore, more dedicated studies are needed to elucidate the underlying complex pathophysiological mechanisms.

The study presented here faced some limitations. The study population comprised young, low-risk Chinese patients diagnosed with ACS. Thus, further investigation is needed to generalize our findings to populations of other ages and races. Although multiple multivariable models were built to establish the independent association of GA with MACCE, information on some important confounders (e.g., proteinuria, adherence to angiotensin-converting enzyme inhibitor, or angiotensin-II receptor blockers) is lacking. Meanwhile, we were unable to determine the causality between GA and adverse outcomes due to the retrospective nature of this study. Considering the low incidence of clinical endpoints during an intermediate-term follow-up, there was not enough statistical power to detect the association between GA and clinical outcomes. Lastly, we were unable to determine the specific reasons for unplanned revascularization, including *native* lesion progression and stent-related restenosis or thrombosis. Intracoronary imaging may provide some information on potential mechanisms related to the role of GA on coronary plaques and arteries.

Conclusion

Increased GA levels in the serum are associated with MACCE in ACS patients after PCI, and this is independent of traditional risk factors and HbA1c, during an intermediate-term follow-up. Measuring GA levels in the serum is not only a method that can be used for glycemic control when using HbA1c is problematic but is also useful to identify ACS patients (particularly patients with preexisting diabetes) who are at an increased risk for future adverse events despite PCI (e.g., GA >15.9%). Future studies are

necessary to investigate the mechanisms behind GA in accelerating the progression of atherosclerosis.

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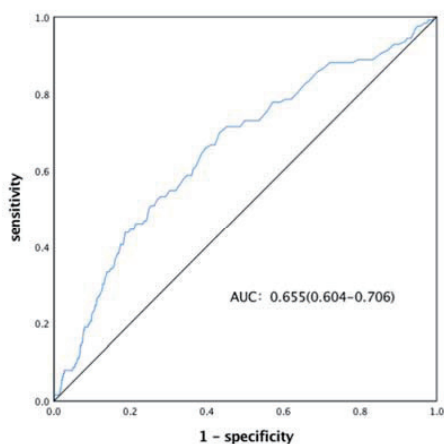
Potential Conflicts of Interest

All authors have no potential conflict of interest to disclose.

References

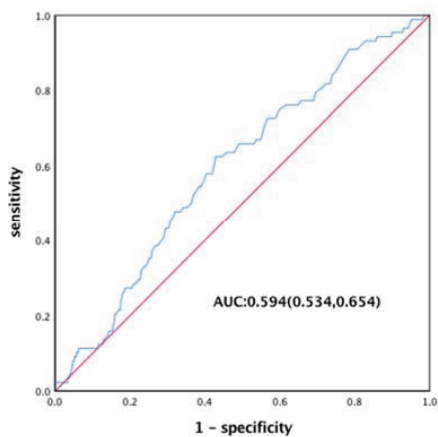
- 1) Sinnaeve PR, Steg PG, Fox KA, Van de Werf F, Montalescot G, Granger CB, Knobel E, Anderson FA, Dabbous OH and Avezum A: Association of elevated fasting glucose with increased short-term and 6-month mortality in ST-segment elevation and non-ST-segment elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. *Arch Intern Med*, 2009; 169: 402-409
- 2) Cakmak M, Cakmak N, Cetemen S, Tanriverdi H, Enc Y, Teskin O and Kilic ID: The value of admission glycosylated hemoglobin level in patients with acute myocardial infarction. *Can J Cardiol*, 2008; 24: 375-378
- 3) Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes care*, 2003; 26: 688-696
- 4) Kurihara O, Takano M, Yamamoto M, Shirakabe A, Kimata N, Inami T, Kobayashi N, Munakata R, Murakami D, Inami S, Okamatsu K, Ohba T, Ibuki C, Hata N, Seino Y and Mizuno K: Impact of prediabetic status on coronary atherosclerosis: a multivessel angioscopic study. *Diabetes care*, 2013; 36: 729-733
- 5) Bergman M, Abdul-Ghani M, DeFronzo RA, Manco M, Sesti G, Fiorentino TV, Ceriello A, Rhee M, Phillips LS, Chung S, Cravalho C, Jagannathan R, Monnier L, Colette C, Owens D, Bianchi C, Del Prato S, Monteiro MP, Neves JS, Medina JL, Macedo MP, Ribeiro RT, Filipe Raposo J, Dorcely B, Ibrahim N and Buysschaert M: Review of methods for detecting glycemic disorders. *Diabetes Res Clin Pract*, 2020; 165: 108233
- 6) Parrinello CM and Selvin E: Beyond HbA1c and glucose: the role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. *Curr Diab Rep*, 2014; 14: 548
- 7) Koga M: Glycated albumin; clinical usefulness. *Clin Chim Acta*, 2014; 433: 96-104
- 8) Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M and Coresh J: Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *Lancet Diabetes Endocrinol*, 2014; 2: 279-288
- 9) Selvin E, Rawlings AM, Lutsey PL, Maruthur N, Pankow JS, Steffes M and Coresh J: Fructosamine and Glycated Albumin and the Risk of Cardiovascular Outcomes and Death. *Circulation*, 2015; 132: 269-277
- 10) Copur S, Siroopol D, Afsar B, Comert MC, Uzunkopru G, Sag AA, Ortiz A, Covic A, van Raalte DH, Cherney DZ, Rossing P and Kanbay M: Serum glycated albumin predicts all-cause mortality in dialysis patients with diabetes mellitus: meta-analysis and systematic review of a predictive biomarker. *Acta Diabetol*, 2021; 58: 81-91
- 11) Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA and White HD: Fourth Universal Definition of Myocardial Infarction (2018). *Circulation*, 2018; 138: e618-e651
- 12) Roohk HV, Zaidi AR and Patel D: Glycated albumin (GA) and inflammation: role of GA as a potential marker of inflammation. *Inflamm Res*, 2018; 67: 21-30
- 13) Mukai N, Ninomiya T, Hata J, Hirakawa Y, Ikeda F, Fukuhara M, Hotta T, Koga M, Nakamura U, Kang D, Kitazono T and Kiyohara Y: Association of hemoglobin A1c and glycated albumin with carotid atherosclerosis in community-dwelling Japanese subjects: the Hisayama Study. *Cardiovasc Diabetol*, 2015; 14: 84
- 14) Pu LJ, Lu L, Shen WF, Zhang Q, Zhang RY, Zhang JS, Hu J, Yang ZK, Ding FH, Chen QJ, Shen J, Fang DH and Lou S: Increased serum glycated albumin level is associated with the presence and severity of coronary artery disease in type 2 diabetic patients. *Circ J*, 2007; 71: 1067-1073
- 15) Shen Y, Pu LJ, Lu L, Zhang Q, Zhang RY and Shen WF: Glycated albumin is superior to hemoglobin A1c for evaluating the presence and severity of coronary artery disease in type 2 diabetic patients. *Cardiology*, 2012; 123: 84-90
- 16) Mihara A, Ohara T, Hata J, Honda T, Chen S, Sakata S, Oishi E, Hirakawa Y, Nakao T, Kitazono T and Ninomiya T: Association between serum glycated albumin and risk of cardiovascular disease in a Japanese community: The Hisayama Study. *Atherosclerosis*, 2020; 311: 52-59
- 17) Kannel WB and McGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes care*, 1979; 2: 120-126
- 18) Mehran R, Dangas GD, Kobayashi Y, Lansky AJ, Mintz GS, Aymong ED, Fahy M, Moses JW, Stone GW and Leon MB: Short- and long-term results after multivessel stenting in diabetic patients. *J Am Coll Cardiol*, 2004; 43: 1348-1354
- 19) Yang ZK, Shen Y, Shen WF, Pu LJ, Meng H, Zhang RY, Zhang Q, Chen QJ, De Caterina R and Lu L: Elevated

- glycated albumin and reduced endogenous secretory receptor for advanced glycation endproducts levels in serum predict major adverse cardio-cerebral events in patients with type 2 diabetes and stable coronary artery disease. *Int J Cardiol*, 2015; 197: 241-247
- 20) Lu L, Jin Pu L, Chen QJ, Wang L, Peng W, Yan X, Zhang Q, Yan Zhang R, Gong PH, Qiu JP and Shen WF: Increased glycated albumin and decreased esRAGE concentrations are associated with in-stent restenosis in Chinese diabetic patients. *Clin Chim Acta*, 2008; 396: 33-37
- 21) Du R, Zhang RY, Lu L, Shen Y, Pu LJ, Zhu ZB, Zhang Q, Hu J, Yang ZK, Ding FH, Zhang JS and Shen WF: Increased glycated albumin and decreased esRAGE levels in serum are related to negative coronary artery remodeling in patients with type 2 diabetes: an Intravascular ultrasound study. *Cardiovasc Diabetol*, 2018; 17: 149
- 22) Shen Y, Lu L, Ding FH, Sun Z, Zhang RY, Zhang Q, Yang ZK, Hu J, Chen QJ and Shen WF: Association of increased serum glycated albumin levels with low coronary collateralization in type 2 diabetic patients with stable angina and chronic total occlusion. *Cardiovasc Diabetol*, 2013; 12: 165
- 23) Yoshiuchi K, Matsuhisa M, Katakami N, Nakatani Y, Sakamoto K, Matsuoka T, Umayahara Y, Kosugi K, Kaneto H, Yamasaki Y and Hori M: Glycated albumin is a better indicator for glucose excursion than glycated hemoglobin in type 1 and type 2 diabetes. *Endocr J*, 2008; 55: 503-507
- 24) Hashimoto K, Tanikawa K, Nishikawa J, Chen Y, Suzuki T and Koga M: Association of variation range in glycated albumin (GA) with increase but not decrease in plasma glucose: implication for the mechanism by which GA reflects glycemic excursion. *Clin Biochem*, 2015; 48: 397-400
- 25) Newsholme P, Cruzat VF, Keane KN, Carlessi R and de Bittencourt PI, Jr.: Molecular mechanisms of ROS production and oxidative stress in diabetes. *Biochem J*, 2016; 473: 4527-4550
- 26) Oka S, Deyama J, Umetani K, Harama T, Shimizu T, Makino A, Sano K and Nakamura M: Glycemic variability is associated with myocardial damage in nondiabetic patients with ST-elevation myocardial infarction. *Cardiovasc Endocrinol Metab*, 2018; 7: 47-53
- 27) Zhang JW, He LJ, Cao SJ, Yang Q, Yang SW and Zhou YJ: Effect of glycemic variability on short term prognosis in acute myocardial infarction subjects undergoing primary percutaneous coronary interventions. *Diabetol Metab Syndr*, 2014; 6: 76
- 28) Pu Z, Lai L, Yang X, Wang Y, Dong P, Wang D, Xie Y and Han Z: Acute glycemic variability on admission predicts the prognosis in hospitalized patients with coronary artery disease: a meta-analysis. *Endocrine*, 2020; 67: 526-534
- 29) Zhao X, Li Q, Tu C, Zeng Y and Ye Y: High glycated albumin is an independent predictor of low response to clopidogrel in ACS patients: a cross-sectional study. *Cardiovasc Diabetol*, 2020; 19: 171
- 30) Morel O, El Ghannudi S, Hess S, Reydel A, Crimizade U, Jesel L, Radulescu B, Wiesel ML, Gachet C and Ohlmann P: The extent of P2Y12 inhibition by clopidogrel in diabetes mellitus patients with acute coronary syndrome is not related to glycaemic control: roles of white blood cell count and body weight. *Thromb Haemost*, 2012; 108: 338-348
- 31) Schoos MM, Dangas GD, Mehran R, Kirtane AJ, Yu J, Litherland C, Clemmensen P, Stuckey TD, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Brodie BR, Mazzaferri EL, Jr., Maehara A and Stone GW: Impact of Hemoglobin A1c Levels on Residual Platelet Reactivity and Outcomes After Insertion of Coronary Drug-Eluting Stents (from the ADAPT-DES Study). *Am J Cardiol*, 2016; 117: 192-200



Glycated albumin level of 15.9% associated with the maximal Youden Index (Sensitivity: 69.8%, Specificity: 56.7%)

Supplemental Fig. 1. The receiver operating characteristic curve shows the prognosis predictive value of glycated albumin in the entire population. AUC, area under the curve



Glycated albumin level of 19.5% associated with the maximal Youden Index (Sensitivity: 62.5%, Specificity: 57.1%)

Supplemental Fig. 2. The receiver operating characteristic curve shows the prognosis predictive value of glycated albumin in a subset of patients with diabetes. AUC, area under the curve