Effect of 1,5-anhydroglucitol levels on culprit plaque rupture in diabetic patients with non-ST segment elevation acute coronary syndrome

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Abstract

Background Postprandial hyperglycemia was reported to play a key role in established risk factors of coronary artery diseases (CAD) and cardiovascular events. Serum 1,5-anhydroglucitol (1,5-AG) levels are known to be a clinical marker of short-term postprandial glucose (PPG) excursions. Low serum 1,5-AG levels have been associated with occurrence of CAD; however, the relationship between 1,5-AG levels and coronary plaque rupture has not been fully elucidated. The aim of this study was to evaluate 1,5-AG as a predictor of coronary plaque rupture in diabetic patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS).

Methods A total of 132 diabetic patients with NSTE-ACS were included in this study. All patients underwent intravascular ultrasound examination, which revealed 38 patients with plaque rupture and 94 patients without plaque rupture in the culprit lesion. Fasting blood glucose (FBS), hemoglobin A1c (HbA1c) and 1,5-AG levels were measured before coronary angiography. Fasting urinary 8-iso-prostaglandin F2α (8-iso-PGF2α) level was measured and corrected by creatinine clearance.

Results Patients with ruptured plaque had significantly lower serum 1,5-AG levels and a tendency of higher HbA1c levels than patients without ruptured plaque in our study population. In multivariate analysis, low 1,5-AG levels were an independent predictor of plaque rupture (odds ratio 3.3; p = 0.006) in diabetic patients with NSTE-ACS, but HbA1c was not. The area under the receiver-operating characteristic curve for 1,5-AG (0.678, p = 0.001) to predict plaque rupture was superior to that for HbA1c (0.618, p = 0.034). Levels of 1,5-AG were significantly correlated with urinary 8-iso-PGF2α levels (r=-0.224, p = 0.010).

Conclusions Serum 1,5-AG may identify high risk for coronary plaque rupture in diabetic patients with NSTE-ACS, which suggests PPG excursions are related to the pathogenesis of plaque rupture in diabetes.

Background

Acute coronary syndromes (ACS), including ST-elevation myocardial infarction (STEMI) and Non-ST-elevation acute coronary syndromes (NSTE-ACS), are a common cause of morbidity and mortality in individuals with diabetes. Autopsy data and intravascular imaging studies have showed that ACS results from spontaneous plaque rupture or erosion and subsequent thrombosis [1, 2, 3]. A meta-analysis, based on optical coherence tomography findings, showed the rate of plaque ruptures is 70.4% in STEMI patients, 55.6% in NSTEMI patients and 39.1% in unstable angina patients, respectively [4]. In an analysis of lesions from patients after sudden coronary death, ruptured plaque is recognized to be responsible for the most of cases of acute coronary thrombi [5]. Diabetic patients are at a high risk for cardiovascular events for having more vulnerable features in both culprit and non-culprit lesions compare to patients without diabetes [6]. Many researchers are attempting to find out what factors could affect coronary plaque rupture in diabetic patients for preventing critical outcomes.

Serum 1,5-anhydroglucitol (1,5-AG) level is a clinical marker to better reflect short-term postprandial hyperglycemia and glycemic variability (GV) than do hemoglobin A_{1c} (HbA_{1c}) level [7]. Therefore, 1,5-AG

levels may be associated with cardiovascular complications in diabetes. Indeed, some studies have reported that 1,5-AG levels are bound up with cardiovascular disease [8, 9]. Several clinical studies showed that 1,5-AG levels had utility to predict cardiovascular events in study population [10, 11, 12]. However, the association between 1,5-AG levels and coronary plaque rupture in diabetic patients with ACS is unclear. In the present study, by using intravascular ultrasound (IVUS), which provides detailed, high-quality tomographic images and can detect plaque rupture in vivo [13], we investigated whether any relation exists between 1,5-AG levels and ruptured plaque in culprit lesion of diabetic patients with NSTE-ACS.

Methods

Patient population and study design

This is a prospective observational study. We included 208 diabetic patients with NSTE-ACS, who were admitted to Shanghai General Hospital Baoshan Branch and Beijing Anzhen Hospital between December 2018 and July 2019. All enrolled patients were admitted and underwent coronary angiography and IVUS in the culprit vessel. Patients with any of the following were excluded from the study: 1) totally occlusive lesions, 2) restenosis after stenting, 3) previous coronary artery bypass graft surgery, 4) severe heart failure (NYHA functional class III or above), 5) renal failure (creatinine clearance < 30 ml/min), 6) hepatic insufficiency, 7) infectious disease, 7) plaques unsuitable for analysis, and 8) insufficient clinical data. A total of 132 patients were included for analysis after excluding 76 patients who meeting the exclusion criteria. 38 patients had coronary plaque rupture in culprit lesion diagnosed by IVUS. NSTE-ACS consisted of non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris, which were defined according to the 2014 ACC/AHA Guideline for NSTE-ACS. Type 2 diabetes mellitus (T2DM) was diagnosed according to the American Diabetes Association criteria or medical history and the use of insulin or glucose-lowering medication. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or treatment with oral antihypertensive drugs. Hyperlipidemia was diagnosed according to the modified National Cholesterol Education Program-Adult Treatment Panel III. The study protocol was approved beforehand by the Medical Ethics Committee of Shanghai General Hospital Baoshan Branch and the Medical Ethics Committee of Beijing Anzhen Hospital, and the procedures followed were in accordance with the institutional guidelines. The study complied with the Declaration of Helsinki, and informed consent was obtained from all patients.

Ivus Imaging Protocol And Analysis

All patients were performed with coronary angiography by standard Judkins technique. IVUS examination was performed using an IVUS system (iLAB™ Ultrasound Imaging System, Boston Scientific, USA) and a 40 MHz intravascular catheter (OptiCross™, Boston Scientific, USA) before any intervention. The IVUS catheter was advanced into the culprit vessel more than 10 mm beyond the culprit lesion and withdrawn at a pullback speed of 0.5 mm/s automatically. In this study, a culprit lesion was defined as the lesion

related to the clinical event, as identified by both coronary angiography and electrocardiogram findings. A ruptured plaque was defined as the plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment. A fragmented and loosely adherent plaque without a distinct cavity and without a fibrous cap fragment was not considered as a plaque rupture [14]. IVUS quantitative analysis was performed by two independent experienced interventional cardiologists who were blinded to the patients' clinical information according to the criteria of the American College of Cardiology Clinical Expert Consensus Document on IVUS.

Laboratory Measurement

We collected blood samples and urine samples from patients after overnight fasting. Samples were stored at -80 °C prior to analysis. Serum levels of 1,5-AG were measured by a colorimetric method (Nippon Kayaku, Tokyo, Japan) using a Lana 1,5-AG auto liquid automatic analyzer (JCA-BM 8060, JEOL Ltd., Tokyo, Japan). Serum concentration of hemoglobin A_{1c} (HbA_{1c}) was determined by high-performance liquid chromatographic method (Tosoh HLC-723G7; Tosoh Corporation, Tokyo, Japan). The urinary 8-iso-$PGF_{2\alpha}$ levels were measured by a competitive enzyme-linked immunosorbent assay (Cayman Chemical, Ann Arbor, MI, USA) and corrected by creatinine clearance. The plasma concentration of fasting blood glucose (FBG), creatinine, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglyceride (TG), the high-sensitivity C-reactive protein (hs-CRP) were measured. The non-HDL-c level was calculated as the TC level minus the HDL-c level.

Statistical analysis

All statistical analyses were performed by using SPSS for Windows 24.0 (SPSS Inc, Chicago, IL, USA). All data were tested for normal distribution with the Kolmogorov-Smirnov test. Data are presented as mean with standard deviation (SD) for continuous distributed variables, frequencies and percentages for categorical variables, and median with 25% and 75% percentiles for abnormal distributed parameters. Differences between two groups were assessed by using the t-tests, Chi square, and Mann-Whitney rank analysis. Correlation between continuous variables was determined by Pearson correlation coefficients. Univariate and multivariate logistic regression analyses were performed to identify independent predictors for ruptured culprit plaque in study population. The predictive value of 1,5-AG and HbA_{1c} for the presence of ruptured plaque in culprit lesion was calculated by constructing receiver-operating characteristic (ROC) curves. A value of $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics of patients

During the study period, 208 diabetic patients with NSTE-ACS underwent CAG and IVUS. We excluded 16 patients with restenosis after stenting, 15 patients with insufficient IVUS data, 5 patients with severe heart

failure, 8 patients with renal failure, 14 patients without 1,5-AG data, and 18 patients with other data loss. Finally, a total of 132 patients were enrolled into the present study. Among of all subjects, 38 patients had culprit plaque rupture detected by IVUS (Rupture group), 94 patients had not (Non-rupture group) (Fig. 1). Compared to patients of non-rupture group, those patients with ruptured plaque had significantly lower 1,5-AG levels (11.6 ± 4.9 vs. 14.6 ± 6.6 μg/ml, P = 0.016), and higher non-HDL-c levels [median (interquartile range): 4.46 (3.81, 4.86) vs. 4.02 (3.61, 4.54) mmol/L, P = 0.045]. Patients with plaque rupture had tendencies of higher hemoglobin A_{1c} (7.2 ± 1.4 vs. 6.7 ± 1.2%, P = 0.075) and urinary 8-iso-$PGF_{2\alpha}$ (140.5 ± 79.3 vs. 116.0 ± 72.1 pmol/mmolCr, P = 0.088) levels compared to patients without plaque rupture. No significant differences were observed between two groups in terms of age, gender, hypertension, hyperlipidemia, body mass index (BMI), blood pressure, left ventricular ejection fraction (LVEF), eGFR, hs-CRP, and medicine treatments (Table 1).

Table 1

Clinical characteristics in the study population

Variables	Rupture	non-Rupture	P value
n	38	94	
Age (years)	59.1 ± 9.2	60.6 ± 10.1	0.429
Males	23 (60.5)	61 (64.9)	0.637
Current smoking	26 (68.4)	50 (53.2)	0.109
Hypertension	28 (73.7)	60 (63.8)	0.277
Hyperlipidemia	27 (71.2)	57 (60.6)	0.260
Duration of diabetes (years)	4.6 ± 4.9	3.8 ± 5.0	0.397
BMI (kg/m^2)	26.4 ± 3.9	25.6 ± 2.6	0.189
LVEF (%)	60.4 ± 7.9	62.3 ± 9.3	0.293
eGFR ($ml/min/1.73\ m^2$)	80.8 ± 27.5	82.2 ± 30.8	0.795
SBP (mmHg)	129 ± 13	131 ± 16	0.488
DBP (mmHg)	76 ± 9	77 ± 10	0.789
TG (mmol/L)	1.82 (1.05, 2.54)	1.78 (0.94, 2.48)	0.548
HDL-C (mmol/L)	0.95 (0.82, 1.26)	1.02 (0.91, 1.23)	0.350
non-HDL-C (mmol/L)	4.46 (3.81, 4.86)	4.02 (3.61, 4.54)	0.045
WBC ($10^9/L$)	7.3 ± 1.6	7.2 ± 1.7	0.934
hs-CRP (mg/dL)	2.01 (1.20, 3.63)	1.18 (0.84, 3.71)	0.116
Urinary 8-iso-$PGF_{2\alpha}$ (pmol/mmolCr)	140.5 ± 79.3	116.0 ± 72.1	0.088
FBG (mmol/L)	8.1 ± 3.2	7.5 ± 2.0	0.214
HbA_{1c} (%)	7.2 ± 1.4	6.7 ± 1.2	0.075
1,5-AG (μg/ml)	11.6 ± 4.9	14.5 ± 6.6	0.016

 Control group was matched for these criteria. Data are given as number (percentage) for categorical variables and mean ± standard deviation or median (IQR) for continuous variables. Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; 8-iso-$PGF_{2\alpha}$, 8-iso-prostaglandin $F_{2\alpha}$; FBG, fasting blood glucose; HbA_{1c}, hemoglobin A_{1c}; 1,5-AG, 1,5-anhydroglucitol; ACEI/ARB, angiotensin-converting-enzyme inhibitor/ angiotensin II receptor blocker

Variables	Rupture	non-Rupture	P value
Medications on admission			
Aspirin	30 (78.9)	70 (74.5)	0.587
Statins	22 (57.9)	62 (66.0)	0.383
ACEI/ARB	20 (52.6)	52 (55.3)	0.779
Oral antidiabetic drugs	29 (76.3)	63 (67.0)	0.293
Insulin	16 (42.1)	32 (34.0)	0.383

 Control group was matched for these criteria. Data are given as number (percentage) for categorical variables and mean ± standard deviation or median (IQR) for continuous variables. Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; 8-iso-$PGF_{2\alpha}$, 8-iso-prostaglandin $F_{2\alpha}$; FBG, fasting blood glucose; HbA_{1c}, hemoglobin A_{1c}; 1,5-AG, 1,5-anhydroglucitol; ACEI/ARB, angiotensin-converting-enzyme inhibitor/ angiotensin II receptor blocker

Angiographic And Ivus Results

Angiographic findings and IVUS analysis were summarized in Table 2. Evaluation of the culprit lesion according to IVUS was possible in all 132 enrolled patients, and plaque rupture was observed in 38 patients (28.8%). There were no significant differences in culprit lesion location and three-vessel disease between plaque rupture and non-rupture groups. IVUS data showed there were not significant differences in lesion volume, length, plaque burden, external elastic membrane cross-sectional areas, lumen cross-sectional areas, plaque plus media cross-sectional areas, and remodeling index between patients with and without plaque rupture.

Table 2

Culprit lesion characteristics assessed by angiography and intravascular ultrasound

Variables	Rupture	Non-rupture	P value
n	38	94	
Angiographic analysis			
Culprit lesion			0.742
LM	1 (2.6)	5 (5.3)	
LAD	13 (34.2)	38 (40.4)	
LCX	6 (15.8)	15 (16.0)	
RCA	18 (47.4)	36 (38.3)	
Lesion location			0.814
Ostial	1(2.6)	6 (6.4)	
Proximal	13 (34.2)	33 (35.1)	
Mild	20 (52.6)	44 (46.8)	
Distal	4 (10.5)	11 (11.7)	
3-vessel disease	15 (39.5)	31 (33.0)	0.478
IVUS analysis			
EEM CSA (mm^2)	20.7 ± 6.5	19.3 ± 5.4	0.204
Lumen CSA (mm^2)	4.3 ± 1.4	4.2 ± 1.0	0.398
P&M CSA (mm^2)	16.4 ± 6.1	15.1 ± 5.4	0.254
Plaque burden (%)	77.6 ± 8.2	76.8 ± 8.5	0.639
Length (mm)	19.2 ± 5.4	18.5 ± 6.8	0.677
Volume (mm^3)	130.5 ± 51.9	125.2 ± 53.3	0.680
Remodeling index	1.01 ± 0.15	0.97 ± 0.19	0.237

Data are given as number (percentage) for categorical variables and mean ± standard deviation. Abbreviations: LM, left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; IVUS, intravascular ultrasound; EEM, external elastic membrane; CSA, cross-sectional areas; P&M, Plaque plus media

Table 3
Independent predictors for ruptured plaque

Variables	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Current smoking	1.908 (0.861, 4.219)	0.112		
Body mass index (> 30 kg/m^2)	2.146 (0.879, 5.235)	0.094		
non-HDL-C (≧ 4.1 mmol/L)	3.236 (1.475, 7.143)	0.003	4.237 (1.767, 10.101)	0.001
hs-CRP (> 3 mg/L)	1.591 (0.649, 3.899)	0.310		
1, 5-AG (Lower tertile, < 10.35 μg/ml)	2.525 (1.129, 5.650)	0.024	3.300 (1.396, 7.752)	0.006
HbA_{1c} (> 7%)	2.028 (0.894, 4.587)	0.091	2.221 (0.912, 5.405)	0.079
Urinary 8-iso-$PGF_{2α}$ (Upper tertile, > 136 pmol/mmolCr)	2.008 (0.921, 4.386)	0.080		
Abbreviations: non-HDL-C, non-high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; 1,5-AG, 1,5-anhydroglucitol; HbA_{1c}, hemoglobin A_{1c}; 8-iso-$PGF_{2α}$, 8-iso-prostaglandin $F_{2α}$				

Relationship Between 1,5-ag Level And Plaque Rupture

We performed univariate and multivariate analysis to determine independent predictors for plaque rupture in culprit lesion. In the multiple regression analysis including all variables with p-value of ≤ 0.10 on univariable analysis, low level of 1,5-AG (lower tertile < 10.35 μg/ml, OR 3.3, 95% CI 1.396–7.752, p = 0.006) and high level of non-HDL-c (≧ 4.1 mmol/L, OR 4.2, 95% CI 1.767–10.101, p = 0.001) were significantly associated with culprit plaque rupture in diabetic patients with NSTE-ACS (Table 4). We constructed a ROC curve for predicting ruptured plaques by 1,5-AG and HbA_{1c} levels in patients. The area under the ROC curve for 1,5-AG (0.678, 95% CI 0.574–0.782; P = 0.001) was superior to that for HbA_{1c} (0.618, 95% CI 0.513–0.723; P = 0.034) (Fig. 2).

Correlation between serum level of 1,5-AG or HbA_{1c} and urinary 8-iso-$PGF_{2α}$ level

A significant negative correlation was noted between serum level of 1,5-AG and urinary 8-iso-$PGF_{2\alpha}$ level (r=-0.224, P = 0.010). There was no significant correlation between the level of HbA_{1c} and the urinary 8-iso-$PGF_{2\alpha}$ level (r = 0.126, P = 0.150) (Fig. 3).

Discussion

Most cases of sudden cardiac death and myocardial infarction arise from thrombotic coronary occlusion following coronary plaque rupture. Diabetic patients had more plaque ruptures and thrombus than non-diabetic patients in ACS, which may be associated with the greater rates of cardiovascular events in diabetes [15]. However, available screening and diagnostic methods are insufficient to identify the victims before the event occurs. The search for noninvasive approach to detect the plaque rupture was encouraged to perform. In our present study, the principal result shows that serum 1,5-AG, as a biomarker of short-term postprandial hyperglycemia and GV, might be an important surrogate marker of coronary plaque rupture in diabetic patients with NSTE-ACS.

1,5-AG is a naturally occurring 1-deoxy form of glucose. As glucose levels surpass the renal threshold for glucosuria (generally around 10 mmol/L), 1,5-AG is excreted in the urine leading to a rapid reduction in serum levels [16]. Therefore, poor glycemic control is associated with low, rather than high, serum 1,5-AG levels. In the present study, we used IVUS to identify plaque rupture in culprit lesion of diabetic patients with NSTE-ACS and found that the 1,5-AG levels were significantly lower in patients with ruptured plaque than in patients without ruptured plaque. Meanwhile, patients with ruptured plaque had higher non-HDL-c levels and tendencies of higher HbA_{1c} levels compared to patients with non-ruptured plaque. Univariate and multivariate logistic regression analyses showed that low 1,5-AG and high non-HDL-c levels were independent predictors of plaque rupture of culprit lesion in diabetic patients with NSTE-ACS. These results indicated that poor glycemic control and dyslipidemia may be associated with the coronary plaque rupture in diabetes. Preliminary data have shown that 1,5-AG could be expected to best reflect postprandial hyperglycemia in moderately controlled patients, and was more sensitive and specific than HbA_{1c} [17]. Furthermore, as PPG increments are the major contributors to GV in T2DM, 1,5-AG may be particularly suited for monitoring postprandial hyperglycemic excursions [18]. Unlike HbA_{1c}, 1,5-AG is not affected by hypoglycemia. As a result, 1,5-AG appears to differentiate patients with extensive PPG excursions despite having similar HbA_{1c} levels. Selvin et al. reported that patients with low 1,5-AG levels had an increased risk of coronary artery disease, stroke, heart failure, and death compared to patients with high 1,5-AG levels [10]. Takahashi et al. reported that low and exacerbated levels of 1,5-AG are associated with cardiac mortality in ACS patients [11]. The study of Fujiwara et al. showed that 1,5-AG was associated with the presence of de novo coronary artery disease in both well-controlled diabetic and non-diabetic patients [8]. Wada et al. found that low 1,5-AG level was associated with the severity of coronary artery calcification [19]. The current study is the first to report that 1,5-AG levels are significantly associated with coronary plaque rupture in diabetic patients with NSTE-ACS. Moreover, the ROC curve analysis showed 1,5-AG displayed more significant value in predicting plaque rupture than HbA_{1c}. These findings may partly explain the results of previous studies that 1,5-AG levels were associated with

cardiovascular outcomes and support the hypothesis that PPG excursions is strongly associated with the atherosclerotic vulnerable plaque process.

Although the identified role of PPG excursions in the pathogenesis of plaque rupture has not been clarified, oxidative stress, inflammation and endothelial dysfunction may be involved in the process. It was demonstrated that glucose excursions increased oxidative stress than chronic hyperglycemia in T2DM [20]. Ceriello et al. showed that targeting postprandial hyperglycemia has the potential to reduce oxidative stress [21]. We have recently reported that glycemic variability, a component of which is PPG excursions, was significantly correlated with oxidative stress measured as urinary 8-iso-$PGF_{2\alpha}$ in patients with ACS [22]. The present study showed that serum 1,5-AG level, but not HbA_{1c}, was strongly correlated with urinary 8-iso-$PGF_{2\alpha}$ level in diabetic patients with NSTE-ACS. This is in accordance with the previous report of Kohata et al. that 1,5-AG is the strong correlate of oxidative stress in patients with T2DM [23], and it suggests that PPG excursions can be more important than mean glucose to induce oxidative stress in diabetes. It has been demonstrated that oxidative stress plays a key role in atherosclerotic plaque progression [24]. Our previous study showed that increased urinary 8-iso-$PGF_{2\alpha}$ levels were closely associated with greater absolute and percent necrotic core volumes of coronary lesions in diabetic patients [25]. In a pathological study by Nishibe et al., 8-iso-$PGF_{2\alpha}$ was found enriched in coronary plaque specimens especially from vulnerable patients, suggesting a crucial role of free radicals in the formation of vulnerable plaques [26]. Yura et al. reported that 8-iso-$PGF_{2\alpha}$ per se could stimulate endothelin-1 mRNA and protein expression in bovine aortic endothelial cells [27]. Endothelin-1 may cause the stimulation of vascular smooth muscle proliferation and formation of macrophage-rich atherosclerotic plaques [28]. In the study of Esposito et al., the results suggested that acute hyperglycemia, and not sustained elevation of blood glucose levels, could exaggerate inflammation by an oxidative mechanism [29]. Teraguchi et al. reported that dynamic glucose fluctuation was positively and significantly associated with $CD14^{bright}$ CD16 + monocytes levels and might be related to coronary plaque rupture in patients with acute myocardial infarction [30]. All these findings suggest that postprandial hyperglycemic excursions may be involved in progression and destabilization of coronary plaques through the preferential increase in oxidative stress, proinflammatory cytokines, and endothelial dysfunction. Optimizing PPG excursions management may be helpful to prevent the rupture of coronary plaque in diabetic patients.

Study limitations

Several study limitations should be considered in the interpretation of the results. First, the sample size was relatively small, so that it may have influenced the results and the statistical analyses. Second, because we evaluated only limited patients who underwent IVUS and didn't meet any exclusion criteria, our results could have been affected by selection bias and cannot be generalized to all patients. Third, the assessment of plaque rupture was made by IVUS in this study. Although it has been demonstrated that IVUS can provide detailed, high-quality tomographic images to detect plaque rupture, it might be likely that some plaque ruptures were undetected. More detailed plaque morphology could be obtained by

combining IVUS with optical coherence tomography (OCT), virtually increasing accuracy for plaque rupture detection. Finally, this is an observational study. The observational nature of analysis means that we cannot infer causality in the associations we have demonstrated. Future longitudinal and prospective studies are needed to address these issues.

Conclusions

Serum 1,5-AG displayed significant value in predicting culprit plaque rupture in diabetic patients with NSTE-ACS. This suggests that PPG excursions are related to the pathogenesis of plaque rupture in diabetes. The manipulation of PPG excursions may provide a potential therapeutic target for preventing plaque rupture.

Declarations

Abbreviations

1,5-AG, 1,5-anhydroglucitol; PPG, postprandial glucose; GV, glycemic variability; NSTE-ACS, non-ST segment elevation acute coronary syndrome; T2DM, type 2 diabetes mellitus; IVUS, intravascular ultrasound; 8-iso-$PGF_{2\alpha}$, 8-iso-prostaglandin $F_{2\alpha}$; FBG, fasting blood glucose; HbA_{1c}, hemoglobin A_{1c}; BMI, body mass index; non-HDL-C, non-high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Medical Ethics Committee of Shanghai General Hospital Baoshan Branch and the Medical Ethics Committee of Beijing Anzhen Hospital. All participants provided written informed consent.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors of the manuscript do not have any closely related papers or manuscripts that have been submitted or published elsewhere and declare that they do not have any competing interests.

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Authors' contributions

GS and SWZ participated in the design of the study. GS and TZ participated in the exercise protocols. MXG, TZ and WFY performed data collection. XXD and GLS performed laboratory measurement. GS performed the statistical analysis and drafted the manuscript. SWZ participated in revising the manuscript. All authors read and approved the final manuscript.

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Figures

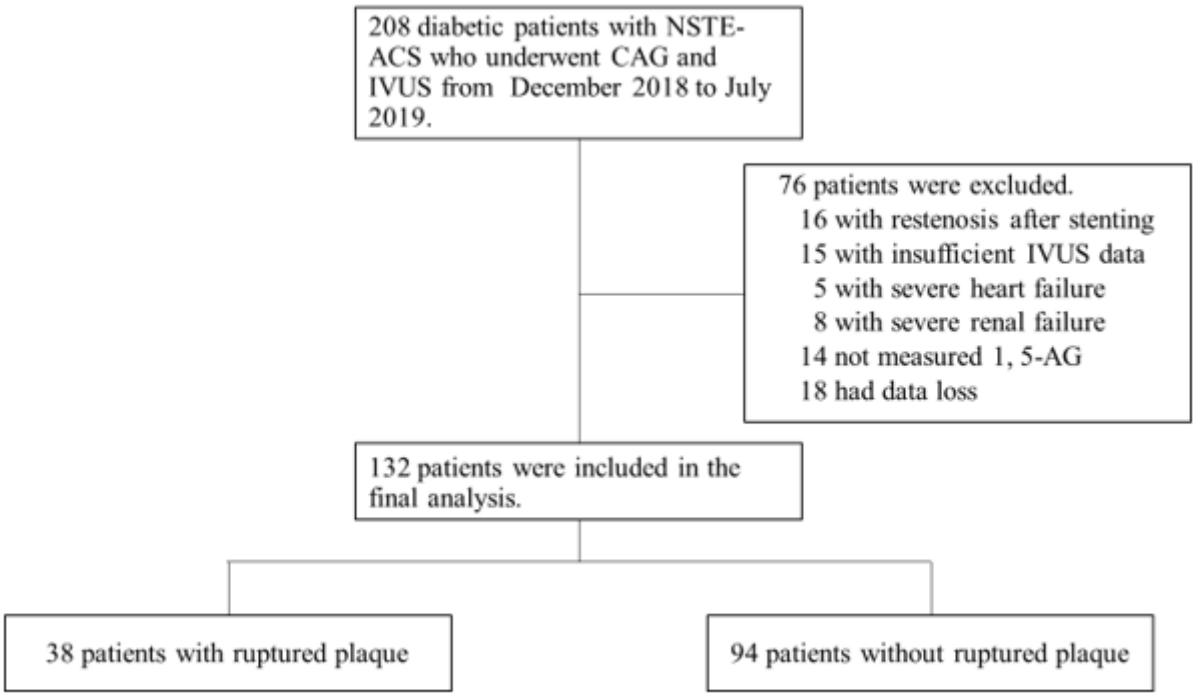

Figure 1

Flow chart of study population.

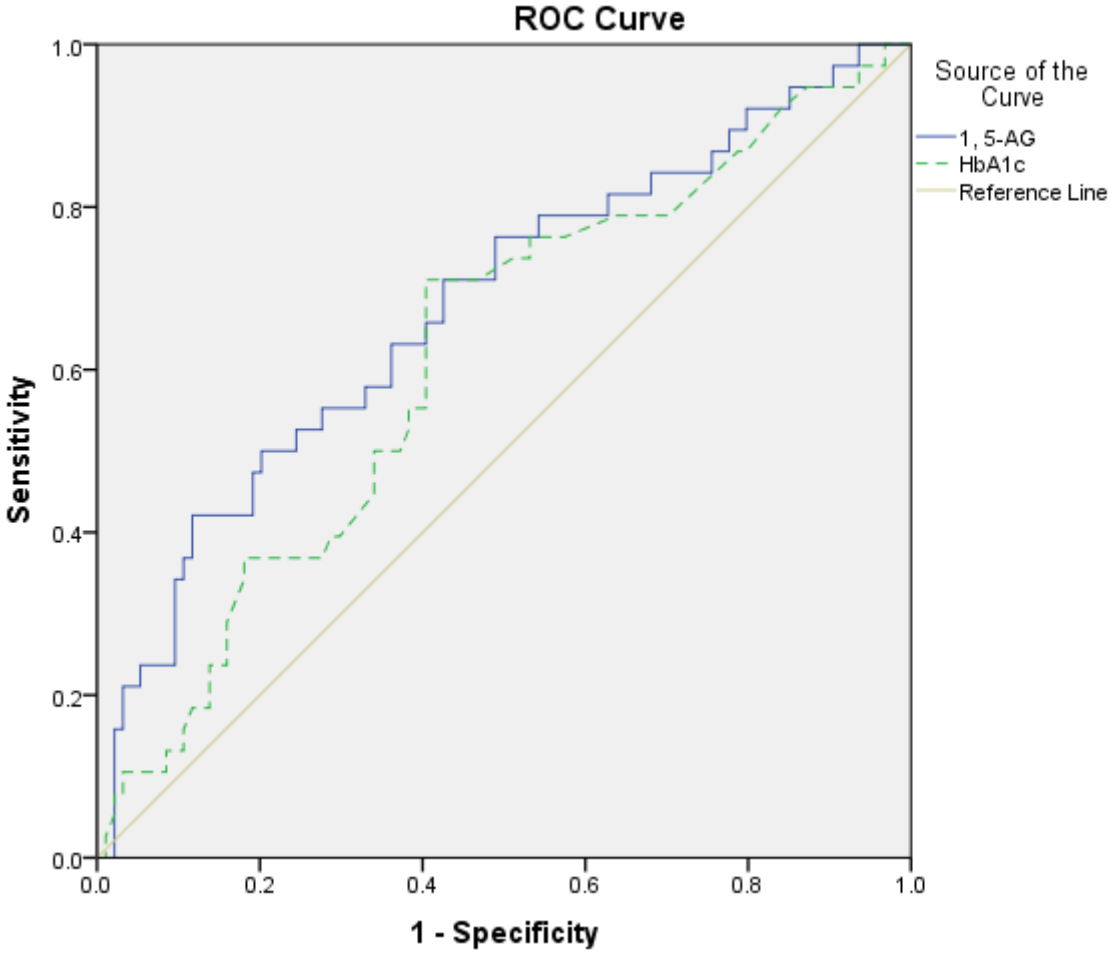

Figure 2

Receiver-operating characteristic curves of 1,5-AG and HbA1c levels to predict coronary plaque rupture in diabetic patients with NSTE-ACS. The areas under the curve of 1,5-AG and HbA1c levels were 0.678 (0.574–0.782, P=0.001) and 0.618 (0.513–0.723, P=0.034), respectively. 1,5-AG, 1,5-anhydro-d-glucitol; HbA1c, hemoglobin A1c.

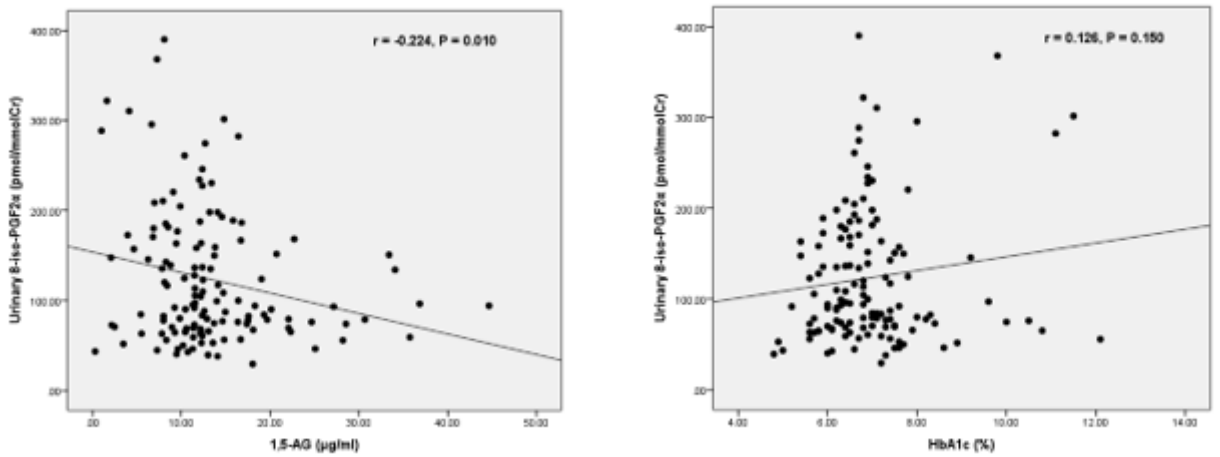

Figure 3

Correlations between serum 1, 5-AG or HbA1c level and urinary 8-iso-PGF2α level in diabetic patients with NSTE-ACS. 1,5-AG, 1,5-anhydro-d-glucitol; HbA1c, hemoglobin A1c; 8-iso-PGF2α, 8-iso-prostaglandin F2α.