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Article

The Association Between Glycemic Disorders and Acute Coronary Syndrome: Plaque Vulnerability in Perimenopausal and Post-Menopausal Women With Diabetes

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Abstract

Aims/Background: Type 2 diabetes mellitus (T2DM) is a well-established risk factor for acute coronary syndrome (ACS). However, the association between prediabetes and ACS remains less clearly characterized, particularly regarding sex-based differences in this association. This study aimed to examine how specific glycemic disorders distinctly influence the risk of plaque erosion and rupture, and to explore sex-based variations in the association. **Methods**: In this cross-sectional study, participants with coronary artery disease (CAD), including ACS and chronic coronary syndrome (CCS), who underwent percutaneous coronary intervention (PCI) with recorded glycemic measurement between 2016 and 2020 were enrolled. Using patients with CCS undergoing PCI as the controls, multivariable logistic regression models were designed to evaluate the association between different glycemic disorders and the risk of ACS manifested as either plaque erosion or rupture. ACS patients with prediabetes and diabetes were respectively matched 1:1 using propensity score matching. The heterogeneity of age, sex and body mass index (BMI) in the association was also investigated. **Results**: Among 1806 screened participants, 1525 participants with recorded glycemic measurement were enrolled in the analysis, consisting of 1158 (75.9%) males with an average age of 65.8 years. With CCS patients undergoing PCI as the controls, compared to participants without diabetes, the associations between prediabetes and diabetes and the risk of ACS were attenuated toward the null after 1:1 propensity score matching. The association between glycemic disorders and ACS was modified by sex (p for interaction = 0.005), rather than age and BMI. Among female participants, 93.7% of whom were over 55 years of age, diabetes was associated with a two-fold higher risk of ACS compared to non-diabetic controls (odds ratio [OR]: 2.06, 95% confidence interval [CI]: 1.02–4.15, p = 0.042). **Conclusion**: The general association between prediabetes and ACS is similar to that in individuals with normal glycemic status. Perimenopausal and post-menopausal women with diabetes may face an elevated risk of plaque erosion or rupture compared to their non-diabetic counterparts, implicating a potential loss of estrogen's plaque-stabilizing effect in the context of glycemic disorders.

Keywords: prediabetes; diabetes; acute coronary syndrome; perimenopause; post-menopausal women

1. Introduction

Acute coronary syndrome (ACS) is an acute clinical manifestation of coronary artery disease (CAD) with significant implications for public health [1,2]. An estimated 7 million people worldwide are diagnosed with acute myocardial infarction each year [3]. ACS remains a leading cause of substantial morbidity and mortality, accounting for over 1 million hospital admissions each year [4]. This substantial disease burden underscores the critical need for optimized prevention and management in high-risk patients.

In recent years, glycemic status has gained significant attention as a major global public health concern, particularly regarding its impact on the incidence of cardiovascular events, including ACS. It has been established that diabetes remains a major risk factor for ACS and an independent predictor of major adverse cardiovascular events (MACE) [5,6]. Although treatments are available for diagnosed diabetes, numerous patients with glycemic disorders, such as undiagnosed diabetes and prediabetes, are still at risk of developing ACS. Previous studies regarding the association between prediabetes and MACE varied due to the heterogeneity of the studied population [7,8]. Clinical evidence indicates a sex-based disparity in ACS risk among patients with diabetes, with women exhibiting a higher risk than men [9,10]. Moreover, patients with severe coronary stenosis were found to host a high burden of metabolic risk factors, which contributed to advanced coronary morbidities [11]. The underlying mechanism of these findings remains to be elucidated, and whether glycemic disorder has a direct adverse effect on plaque erosion or rupture needs to be investigated.

Herein, our study aims to investigate the association between different glycemic statuses and plaque erosion or rupture compared with normal glycemic status, using patients with chronic coronary syndrome (CCS) undergoing

percutaneous coronary intervention (PCI) as the controls. Furthermore, we will investigate how the association between variable glycemic status and ACS risk is influenced by key modifiers. Finally, clarifying sex-based disparities across specific glycemic disorders is another aim of this analysis, with direct implications for developing tailored interventions and improving personalized ACS management in clinical practice.

2. Methods

2.1 Study Design and Population

In this cross-sectional study, ACS and CCS participants with coronary stenosis undergoing percutaneous coronary intervention (PCI) with complete glycemic measurement data at the Department of Cardiology, Huashan Hospital, Fudan University between 2016 and 2020 were enrolled. CCS patients, diagnosed based on the presence of stable angina, compatible electrocardiography (ECG) changes, and a negative serum cardiac troponin level, with coronary stenosis requiring PCI were enrolled. Data from biochemistry lab results, and the severity of coronary stenosis defined by Coronary Artery Disease Reporting and Data System (CAD-RADS) were extracted from the electronic medical records. Medical history and medication use were obtained from both clinical consultation by the cardiologists and electronic medical records documented upon admission.

2.2 ACS Diagnosis

The study enrolled patients with ACS, consisting of ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and unstable angina. The diagnosis was confirmed by cardiologists at the Huashan Hospital based on symptoms involving unstable chest discomfort and chest pain, changes in serum cardiac troponin level and ECG according to the 2018 global myocardial infarction definition [5]. Coronary artery angiography (CAG) was implemented to estimate the degree of coronary artery stenosis and guide PCI in ACS.

2.3 Exposure and Covariates

Glycemic status was divided into three categories including diabetes, prediabetes and non-diabetes. Diabetes was defined as a type 2 diabetes mellitus (T2DM) diagnosis before the hospital admission, regardless of receiving anti-glycemic therapy. Newly diagnosed T2DM met the criteria of glycated hemoglobin (HbA1c) $\geq$6.5% or fasting plasma glucose (FPG) $\geq$7.0 mmol/L. Prediabetes was defined as the absence of diabetes at baseline, with admission laboratory parameters meeting any of the following criteria: HbA1c ranged 5.7%–6.4% or FPG ranged 5.6–6.9 mmol/L. Non-diabetes was classified as the individuals with no history of diabetes and whose admission metrics were as follows: FPG $<$5.6 mmol/L, and glucose $<$7.8 mmol/L after 2-hour after the meal, and HbA1c $<$5.7%. Information about baseline characteristics was obtained from the electronic medical records measured at the time of hospital admission. Body mass index (BMI) was calculated using body weight and height measured by the medical staff.

2.4 Statistical Analysis

Continuous variables were expressed as mean (standard deviation [SD]) if normally distributed or as median (interquartile ranges [IQR]) if skewed, based on the Shapiro–Wilk test. Categorical variables were presented as absolute numbers and percentages (%). All the baseline characteristics of participants across the diabetes, prediabetes and non-diabetes categories were compared using analysis of variance (ANOVA) and Kruskal-Wallis tests for continuous variables, and Chi-square tests for categorical variables. Homogeneity of variance was assessed using Levene or Brown-Forsythe test, as appropriate.

Patients with CCS undergoing PCI formed the control group. The associations between glycemic disorders and ACS were evaluated by multivariable logistic regression, adjusted for age (years), sex (male/female), BMI (kg/m^2), hypertension (yes/no), low-density lipoprotein level (mmol/L), triglyceride level (mmol/L), statin use (yes/no), and history of chronic heart failure (yes/no), acute heart failure (yes/no), stroke (yes/no), and atrial fibrillation (yes/no). Multivariable logistic regression models including interaction terms were used to further show the effect modification by sex, age and BMI. For sensitivity, 1:1 propensity-score matching was performed using the nearest-neighbor method with a caliper width of 0.03, separately comparing prediabetes and normal blood glucose with diabetes and normal blood glucose (**Supplementary Tables 1,2**). The propensity score was calculated using logistic regression, modeling prediabetes or diabetes as the outcome and other potential confounders as covariates (**Supplementary Figs. 1–4**). Subgroup analyses were conducted to examine potential heterogeneity of age, sex and BMI in the association between glycemic disorders and ACS, using normal glycemic status as the reference.

To verify the robustness of the associations, an additional analysis was conducted by reclassifying participants with prediabetes using different criteria based on HbA1c (5.7%–6.4%), FPG (5.6–6.9 mmol/L), or both. Multivariable models were applied using continuous HbA1c and FPG levels to further assess the association between glucose metabolism and ACS in patients without previously diagnosed diabetes at this admission. All data were analyzed using STATA version 17.0 (StataCorp LLC, College Station, TX, USA) and the cobalt package version 4.5.1 in R software version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Diagnosis of multicollinearity among the variables in the multivariate model has been done by function "vif" from the car package in R 4.0.3, and the VIF of covariates was computed for each multiple regression. All VIF values were under 5.0, indicating no evidence of substantial multicollinearity among the covariates in regres-

sions. p-values < 0.05 were considered statistically significant. Given that the proportion of missing data for all primary clinical variables was minimal (<1%), a complete-case analysis was used by excluding the few incomplete entries.

3. Results

3.1 Baseline Characteristics

In this cross-sectional study, 1806 patients with CAD were initially screened. After excluding 281 cases due to insufficient glycemic data for group classification (Fig. 1), a total of 1525 participants were enrolled, with a mean age of 65.8 years (SD = 11.2 years). Among them, 75.9% were male with the mean BMI of 24.9 (SD = 3.3 kg/m^2), and the percentage of ACS was 27.6%. The prevalence of ACS did not differ among people with different glycemic disorders ($p = 0.126$). More participants with prediabetes and T2DM had a history of hypertension ($p < 0.001$). The history of stroke, chronic heart failure and atrial fibrillation did not differ significantly in different glycemic disorders. Participants with diabetes had significantly lower levels of high-density lipoprotein (HDL) ($p < 0.001$), apoprotein A ($p = 0.002$), low-density lipoprotein (LDL) ($p < 0.001$) and apoprotein B ($p = 0.007$), contributing to higher dosage of statin use (42.5% vs 40.3%). The uric acid level of patients with diabetes was lower than those of patients without diabetes and prediabetes, and the difference was statistically significant. The difference may be related to medication use. However, we did not record the use of urate-lowering drugs in enrolled patients. The use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) was more prevalent in participants with T2DM and prediabetes ($p = 0.001$) (Table 1).

3.2 Associations of Glycemic Disorder With ACS

Logistic regression models were used to assess the association between glycemic disorders and ACS. In the univariate model, participants with prediabetes were negatively associated with ACS (odds ratio [OR] 0.75, 95% confidence interval [CI] 0.57–0.99, $p = 0.042$) compared to those with normal glycemic status. After adjusting for age, sex, BMI and hypertension, the association between prediabetes and ACS remained consistent (OR 0.74, 95% CI 0.56–0.98, $p = 0.038$). The association remained significant in the multivariable model (OR 0.73, 95% CI 0.55–0.99, $p = 0.042$) after further adjustment for lipid metabolites, statin use and other cardiovascular disease history. However, among participants with diabetes, no significant association with ACS was observed in any model or in subgroups stratified by the severity of coronary artery stenosis (Table 2, **Supplementary Table 3**). Following propensity score matching, the association between prediabetes and ACS was attenuated towards the null (OR 0.88, 95% CI 0.64–1.21, $p = 0.416$), while the association between diabetes and ACS remained non-significant (OR 1.27, 95% CI 0.94–1.73, $p = 0.122$) (Table 2).

3.3 Subgroup Analysis

In the subgroup analysis, the interactions of age and BMI with glycemic disorders on ACS were generally non-significant. However, a significant effect modification by sex was observed ($p_{\text{interaction}} = 0.005$). The multivariable model showed a significant negative association between prediabetes and ACS among male participants compared to those without diabetes. Of note, female participants with diabetes showed a significantly elevated risk of ACS (OR: 2.06, 95% CI: 1.02–4.15, $p = 0.042$); 93.7% of them were over 55 years of age (Table 3).

3.4 Additional Analysis

To further investigate the association between prediabetes and ACS, an additional analysis was conducted by reclassifying people with prediabetes using HbA1c (5.7%–6.4%), FPG (5.6–6.9 mmol/L), or both. After adjustment for age, sex, BMI, hypertension, LDL, triglycerides levels, statins usage and other cardiovascular disease history, prediabetes participants with HbA1c levels between 6.0%–6.4% showed a negative association with ACS (**Supplementary Table 4**). When prediabetes was defined solely by FPG levels, no significant association with ACS was observed. To further assess the association between glucose metabolism and ACS, we analyzed continuous HbA1c and FPG levels in all participants with no diabetes at admission (including normal glycemic status and prediabetes). After multivariable adjustment, a positive association between FPG and ACS (OR 1.15 per one unit increase, 95% CI 1.05–1.27, $p = 0.003$) was observed, whereas HbA1c level was not linearly associated with odds of ACS (**Supplementary Table 5**).

4. Discussion

4.1 Our Results

According to the results of propensity score matching analysis, there was no significant association between prediabetes and ACS, suggesting that early glycemic disorder may not directly contribute to plaque erosion or rupture, partly due to the inadequacy of related inflammatory response to compromise the plaque stability. In subgroup analysis, although the interaction of age, BMI and glycemic disorders with ACS was generally non-significant, a significant effect modification by sex was observed. Elderly women with diabetes showed a positive association with ACS compared to those with no diabetes, suggesting that estrogen deficiency may be a key contributor to increased plaque vulnerability beyond the effects of aging. Moreover, among participants without diabetes and prediabetes, elevated FPG was significantly associated with an increased risk of ACS, indicating an interaction between elevated blood glucose and stress response of ACS.

Table 1. Baseline characteristics.

	No DM	Prediabetes	DM	Total	*p*-value	F/H/Chi-square
	n = 447	n = 575	n = 503	n = 1525		
Age (years)	64.4 (11.5)	66.4 (11.0)	66.4 (11.1)	65.8 (11.2)	0.008	4.77
Male	341 (76.3%)	458 (79.7%)	359 (71.4%)	1158 (75.9%)	0.006	10.11
BMI (kg/m^2)	24.9 (3.4)	24.9 (3.2)	25.1 (3.4)	24.9 (3.3)	0.436	0.83
Acute coronary syndrome	137 (30.6%)	144 (25.0%)	140 (27.8%)	421 (27.6%)	0.126	4.15
Medical History						
Hypertension	300 (67.1%)	404 (70.3%)	397 (78.9%)	1101 (72.2%)	<0.001	18.17
Chronic heart failure	29 (6.5%)	36 (6.3%)	45 (8.9%)	110 (7.2%)	0.184	3.39
Stroke	37 (8.3%)	50 (8.7%)	50 (9.9%)	137 (9.0%)	0.640	0.89
Atrial fibrillation	20 (4.5%)	24 (4.2%)	27 (5.4%)	71 (4.7%)	0.635	0.91
CAD-RADS categories					0.411	6.11
3	22 (4.9%)	24 (4.2%)	16 (3.2%)	62 (4.1%)		
4A	268 (60.0%)	336 (58.4%)	282 (56.1%)	886 (58.1%)		
4B	54 (12.1%)	88 (15.3%)	76 (15.1%)	218 (14.3%)		
5	103 (23.0%)	127 (22.1%)	129 (25.6%)	359 (23.5%)		
Lab results						
HbA1c (%)	5.70 (5.50–6.50)	6.00 (5.90–6.20)	7.40 (6.65–8.40)	6.20 (5.80–7.00)	<0.001	577.36
Fasting glucose (mmol/L)	5.20 (4.85–6.90)	5.70 (5.10–6.20)	7.20 (5.90–9.40)	5.80 (5.10–7.20)	<0.001	259.25
Uric acid (mmol/L)	0.36 (0.30–0.41)	0.35 (0.29–0.42)	0.34 (0.28–0.41)	0.35 (0.29–0.42)	0.021	7.75
HDL (mmol/L)	0.98 (0.84–1.17)	0.99 (0.85–1.15)	0.94 (0.80–1.09)	0.97 (0.83–1.13)	<0.001	19.15
LDL (mmol/L)	2.4 (0.8)	2.4 (0.9)	2.2 (0.9)	2.3 (0.9)	<0.001	8.05
Triglyceride (mmol/L)	1.44 (1.08–2.04)	1.40 (1.01–1.92)	1.49 (1.05–2.17)	1.43 (1.04–2.06)	0.815	5.02
Albumin (g/L)	41.00 (38.00–43.00)	41.00 (38.00–43.00)	41.00 (38.00–43.00)	41.00 (38.00–43.00)	0.892	0.23
LDH (U/L)	189.00 (161.00–227.00)	184.00 (160.00–221.00)	184.00 (159.00–217.00)	186.00 (160.00–221.00)	0.178	3.46
ApoA (g/L)	1.0 (0.3)	1.0 (0.2)	0.9 (0.2)	0.9 (0.2)	0.002	6.24
ApoB (g/L)	0.62 (0.51–0.76)	0.59 (0.48–0.74)	0.58 (0.47–0.72)	0.60 (0.48–0.74)	0.007	10.05
Lp(a) (mg/dL)	133.00 (63.00–293.00)	121.00 (50.00–276.00)	122.00 (52.00–285.00)	125.00 (55.00–283.00)	0.192	3.30
Serum creatinine (μmol/L)	75 (66–87)	77 (67–90)	76 (63–93)	76 (65–89)	0.319	2.28
Medication use						
Statins use	180 (40.3%)	233 (40.5%)	214 (42.5%)	627 (41.1%)	0.726	0.64
Beta blockers	129 (28.9%)	165 (28.7%)	163 (32.4%)	457 (30.0%)	0.345	2.13
ACEI/ARB	116 (26.0%)	207 (36.0%)	179 (35.6%)	502 (32.9%)	0.001	13.92
Anti-platelet drugs	353 (79.0%)	444 (77.2%)	405 (80.5%)	1202 (78.8%)	0.415	1.76

Abbreviations: DM, diabetes mellitus; BMI, body mass index; CAD-RADS, Coronary Artery Disease Reporting and Data System; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDH, lactate dehydrogenase; ApoA, apolipoprotein A; ApoB, apolipoprotein B; Lp(a), lipoprotein(a); ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers. CAD-RADS 3 is typically 50%–69%, CAD-RADS 4A is 70%–99%, CAD-RADS 4B is left main artery >50% or >70% stenosis in three arteries and CAD-RADS 5 is total occlusion/near total occlusion.

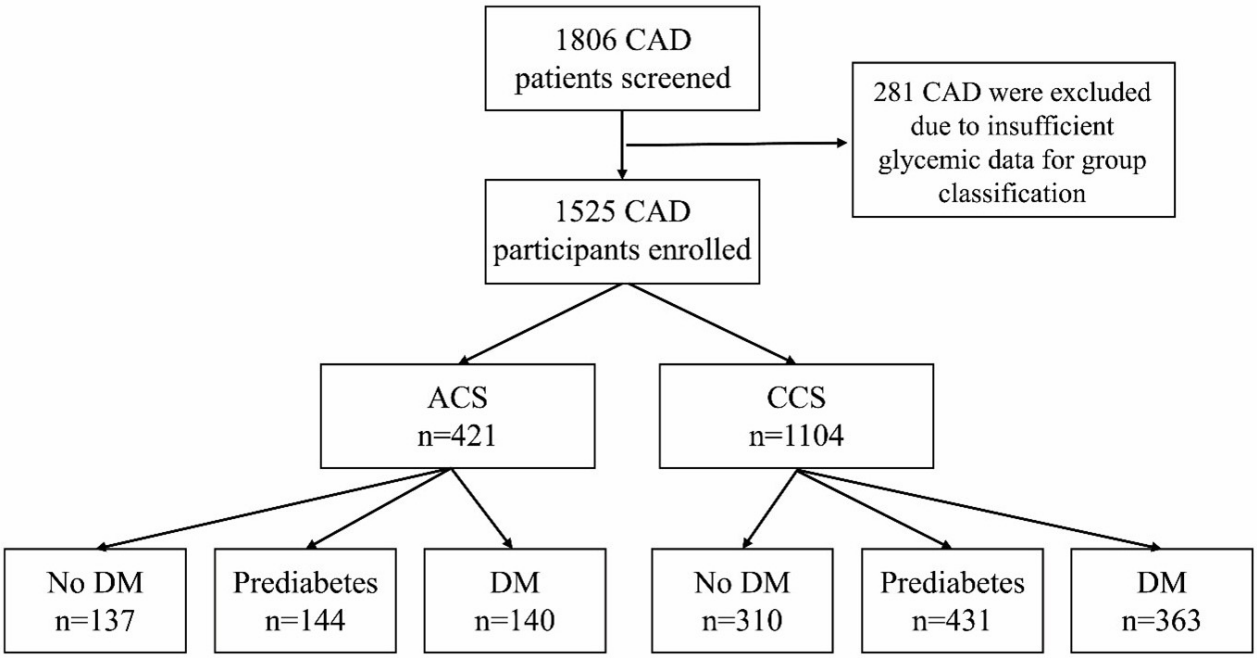

Fig. 1. Flowchart for the selection of enrolled participants. CAD, coronary artery disease; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DM, type 2 diabetes mellitus.

4.2 Previous Studies & Mechanism

Previous studies described the association between glycemic disorders with ACS in patients with severe coronary stenosis. A prospective cohort study showed that the incidence of ACS in patients with CAD and prediabetes did not differ from those with normal glycemic status [8], which is consistent with our findings. A retrospective cohort study from Spain revealed that prediabetes, as determined by HbA1c (5.7%–6.5%), was not associated with ACS in patients with CAD [12]. However, the result exhibited wide confidence interval due to a limited sample size. Our study, with a larger cohort, replicated their findings. Previous studies have indicated a significantly higher risk of ACS in diabetic patients compared to non-diabetic individuals, whether this is attributable to dysglycemia itself warrants further investigation. Diabetic patients typically present with multiple ACS risk factors, such as hypertension and dyslipidemia, which are direct contributors to plaque rupture or erosion. In contrast, the systemic metabolic inflammatory response induced by diabetes likely exerts a far greater impact on plaque stability than dysglycemia per se. In this analysis, prediabetic participants showed similar rates of hypertension, LDL control levels, and statin use to non-diabetic subjects. Moreover, prediabetes may induce a metabolic inflammatory response that is insufficient to compromise plaque stability, thereby explaining the negative findings observed in this study.

For the biomarkers of glucose metabolism, we found that continuous HbA1c level was not linearly associated with log odds of ACS. Besides, we found that participants with HbA1c levels ranging from 6.0% to 6.4% were negatively associated with ACS compared to those with HbA1c <5.7%. Liu et al. [13] found the U-shape relationship between HbA1c level and all-cause mortality among patients with CAD. Specifically, participants with HbA1c levels ranging from 5.7% to 6.7% demonstrated the lowest risk of all-cause death, especially in male patients, which is in accordance with our findings. Previous studies showed that rigorous HbA1c levels (below the prediabetes threshold) may lead to increased risk of adverse cardiovascular events [14,15]. Extremely low HbA1c levels were correlated with alterations in red blood cell indices, increased heme release and disturbances in high-density lipoprotein cholesterol (HDL-C) metabolism [16,17]. These factors were shown to be correlated with coronary atherosclerosis. Our findings highlight the need for further research to investigate the HbA1c range for CAD patients that minimizes the risk of plaque rupture, taking into account other established cardiovascular risk factors.

In our subgroup analysis, men with prediabetes were significantly associated with fewer ACS occurrences compared with those without diabetes. For lifestyle, men were more likely than women to achieve more physical activity targets and participate in cardiac rehabilitation programs [9], which may help explain why the association between poor glycemic control and ACS occurs less pronounced in men. The subgroup analysis demonstrated that most of the women with diabetes were in the perimenopausal and post-menopausal stages, and faced a two-fold higher risk of plaque rupture or erosion compared with their non-diabetic counterparts. This aligns with established evidence demonstrating that the risk of cardiovascular disease rises signif-

Table 2. Regression models for the association between glycemic disorders and acute coronary syndrome (ACS).

	Odds ratio (95% CI)	*p*-value	β value	SE
Crude Model				
No DM	Reference			
Prediabetes	0.75 (0.57–0.99)	0.042	–0.286	0.141
DM	0.87 (0.66–1.15)	0.318	–0.143	0.147
Model 1[a]				
No DM	Reference			
Prediabetes	0.74 (0.56–0.98)	0.038	–0.296	0.142
DM	0.93 (0.70–1.23)	0.610	–0.074	0.145
Model 2[b]				
No DM	Reference			
Prediabetes	0.73 (0.55–0.99)	0.042	–0.309	0.152
DM	0.99 (0.73–1.36)	0.972	<0.001	0.158
Propensity score matching analysis				
No DM	Reference			
Prediabetes	0.88 (0.64–1.21)	0.416	–0.132	0.163
DM	1.27 (0.94–1.73)	0.122	0.241	0.156

[a] Adjusted for age, sex, BMI and hypertension.

[b] Adjusted for age, sex, BMI, hypertension, low density lipoprotein, triglyceride level, statins use, chronic heart failure history, acute heart failure history, stroke history, and atrial fibrillation history.

SE, standard error; CI, confidence interval.

Table 3. Subgroup analysis between glycemic disorders and acute coronary syndrome.

	Glycemic disorders	Adjusted odds ratio	*p*-value	$p_{interaction}$
Age (years)				0.524
	No DM	Reference		
<65	Prediabetes	0.77 (0.49–1.20)	0.244	
	DM	0.87 (0.54–1.41)	0.580	
	No DM	Reference		
≥65	Prediabetes	0.79 (0.52–1.20)	0.271	
	DM	1.13 (0.74–1.72)	0.579	
Sex				0.005
	No DM	Reference		
Male	Prediabetes	0.71 (0.51–0.99)	0.041	
	DM	0.79 (0.56–1.13)	0.206	
	No DM	Reference		
Female	Prediabetes	0.93 (0.43–2.01)	0.862	
	DM	2.06 (1.02–4.15)	0.042	
BMI (kg/m^2)				0.907
	No DM	Reference		
<25	Prediabetes	0.80 (0.53–1.19)	0.271	
	DM	0.98 (0.65–1.50)	0.941	
	No DM	Reference		
≥25	Prediabetes	0.68 (0.43–1.06)	0.091	
	DM	0.99 (0.63–1.58)	0.990	

Adjusted for age, sex, BMI, hypertension, low density lipoprotein, triglyceride level, statins use, chronic heart failure history, acute heart failure history, stroke history, and atrial fibrillation history.

icantly during the menopausal transition compared to the first five decades of a woman's life, a risk that is further amplified by diabetes. However, the direct effect of this transition on plaque rupture or erosion remains unclear, and our study addresses this gap to some extent. As reported, women during the menopause phase may be associated with

a high prevalence of hypertension, dyslipidemia and insulin resistance. Furthermore, the shift toward a more equal estrogen-to-testosterone ratio during this period has been proven to be associated with vasoconstriction, an increased pro-inflammatory response and strengthened chronic cellular senescence. These pathways elevate cardiovascular risk in menopausal women [18]. Thus, glycemic control and the management of related metabolic disorders should be prioritized more rigorously than in men for ACS prevention among women with diabetes near menopause.

We also found that continuously higher FPG was positively associated with ACS among people without a history of diabetes. We hypothesized that elevated FPG levels in individuals without diabetes may be attributed to the stress response associated with ACS. A cohort study by Ye et al. [19] showed that compared to HbA1c, increased FPG level may have a more adverse effect among people with diabetes and CAD. Our study further extrapolated the results among people with no diabetes and prediabetes. FPG is associated with stress hyperglycemia [20], ruling out the influence of diet, which is closely related to high free fatty acids, insulin resistance, steroid levels and oxidative-stress-related damage within somatic cells [21]. Cui et al. [22] pointed out that stress hyperglycemia and FPG level itself were both associated with in-hospital mortality, regardless of patients' diabetic status.

4.3 Limitations

There were several limitations in our study. First, this cross-sectional study could only reveal an association but not a causal relationship between glycemic status and ACS. Second, this single-center study was conducted in Huashan Hospital, and its results, while primarily reflecting the patient demographics of southeastern China and may be extrapolated to similar populations in this region, are not generalizable to all of China. Third, some residual confounders may have been underestimated (including heart failure classification, and personal lifestyle factors), which could introduce bias to our results. Furthermore, it should be noted that the reported association between diabetes and increased ACS risk in postmenopausal women was derived from a small subgroup analysis and lacked supporting hormone data. These limitations preclude definitive conclusions and warrant cautious clinical interpretation.

5. Conclusion

The association between prediabetes and increased risk of ACS does not differ from that of normal glycemic status, indicating a non-positive association of early glycemic disorder in promoting plaque erosion or rupture. Elderly female patients with diabetes face a two-fold higher risk of ACS compared to their non-diabetic female counterparts, suggesting that estrogen deficiency may contribute to increased plaque vulnerability in this population. We propose that precise prevention strategies must emphasize rigorous glycemic control and management of concomitant metabolic disorders for ACS among women with CCS in peri- and postmenopausal phases and those with severe coronary artery stenosis.

Key Points

- The potential effect of prediabetes on the risk of plaque erosion or rupture remains unclear and warrants further investigation.
- Female diabetic participants over 55 years of age exhibited a two-fold increased risk of plaque erosion or rupture compared to non-diabetic counterparts, a significant association that was not observed in male participants.
- The pathophysiological mechanisms linking estrogen deficiency across different glycemic disorder stages to plaque erosion or rupture require further investigation.

Abbreviations

ACS, acute coronary syndrome; CCS, chronic coronary syndrome; Apo, apolipoprotein; BMI, body mass index; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease Reporting and Data System; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus.

Availability of Data and Materials

Data are available on reasonable request from the corresponding author.

Author Contributions

RCL and CS contributed to the statistical analysis, interpretation of data and manuscript writing. YJS, YJY, KY, QZ, JJP, ZDZ, HCN, WS, JL, XPL, HMS and YL were involved in recruitment of participants. YJY, KY, QZ contributed to sample measurement and data analysis. LWB revised the manuscript. All authors contributed to results interpretation. RCL, CS and LWB contributed to the conception, design of the study. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study protocol was designed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Huashan Hospital, Fudan University (No.KY2020-050). They provided informed consent upon admission to the hospital.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM54927.

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