

Impact of Hyperinsulinemia on Long-Term Clinical Outcomes of Percutaneous Coronary Intervention in Patients without Diabetes Who Have Acute Myocardial Syndrome

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Background and Objectives: Hyperinsulinemia plays a key role in the development of cardiovascular impairment in patients with metabolic syndrome. The aim of this study was to evaluate the influence of hyperinsulinemia on long-term clinical outcomes of percutaneous coronary intervention (PCI) in patients without diabetes mellitus who have acute myocardial syndrome (ACS).

Methods: Between March 2016 and January 2019, we enrolled 468 patients with ACS and without diabetes mellitus who received primary PCI. Patients were divided into a low-insulin group (n = 157), medium-insulin group (n = 154), and high-insulin group (n = 157) according to tertiles of fasting insulin level. The primary endpoint was major adverse cardiac events (MACE; all-cause death, non-fatal myocardial infarction, target vessel revascularization [TVR]) at 24 months. The secondary endpoint was angina hospitalization.

Results: Patients in the high-insulin group had an unfavorable prognosis, with a higher rate of MACE (34.39%) than the low-insulin group (22.29%) and medium-insulin group (23.37%) at 24 months ($P < 0.05$). This difference was mainly driven by the increase in TVR. The high-insulin group also had a higher rate of angina hospitalization than the low-insulin group. Cox proportional hazards regression showed that high-insulin level (hazard ratio [HR] 1.870, 95% confidence interval [CI] 1.202–2.909), small-vessel lesion (HR 1.713, 95% CI 1.111–2.642), bifurcation lesion (HR 3.394, 95% CI 2.033–5.067), SYNTAX score (HR 1.084, 95% CI 1.039–1.130), and stent length (HR 1.017, 95% CI 1.002–1.032) increased the incidence of MACE in patients with ACS and without diabetes who underwent PCI.

Conclusion: Hyperinsulinemia might be a valid predictor of clinical outcomes in patients with ACS undergoing PCI.

Keywords: percutaneous coronary intervention, hyperinsulinemia, acute myocardial syndrome, major adverse cardiac events

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Introduction

Metabolic syndrome (MetS) has a high prevalence worldwide.¹ MetS is associated with the development of coronary atherosclerosis, plaque instability, and cardiovascular events in patients with and without type 2 diabetes.^{2,3} The core components of MetS are insulin resistance (IR) and hyperinsulinemia.⁴ A new concept of selective IR proposes that tissues become resistant to the effect of insulin on glucose transport but remain sensitive to its lipogenic effect.⁵ IR may be

compensatory in the body's response to preventing MetS. Hyperinsulinemia is more common than IR and may play a primary role in the development of cardiovascular impairment in patients with MetS.⁶

Previous studies show that hyperinsulinemia is associated with hypertension, obesity, and dyslipoproteinemia, which are risk factors for coronary artery disease.^{7,8} Other studies have indicated that hyperinsulinemia interferes with arteriolar vasodilation and bioavailability of nitric oxide (NO) in obese, insulin-resistant, and healthy individuals.^{4,9} Our previous study demonstrated that hyperinsulinemia impairs the functions of endothelial progenitor cells, which play a key role in maintaining endothelial function and vascular repair.¹⁰ However, the impact of hyperinsulinemia on major clinical outcomes following percutaneous coronary intervention (PCI) is largely unknown.

The aim of this study was to evaluate the impact of hyperinsulinemia on major clinical outcomes in patients with acute myocardial syndrome (ACS) undergoing PCI. Many studies have shown that diabetes mellitus is associated with ischemic events in patients undergoing PCI.^{11–13} Therefore, to avoid the influence of hyperglycemia on clinical outcomes of PCI, we excluded patients with diabetes mellitus in this study.

Methods

Study Population

This was a retrospective observational study. Between March 2016 and January 2019, patients with ACS who received PCI were retrospectively enrolled. The inclusion criteria were 1) patients at least 18 years old who had ACS; ACS was defined as ST segment elevated myocardial infarction (STEMI), non-ST segment elevated myocardial infarction (MI), and unstable angina.¹⁴ 2) Patients who underwent primary PCI with a drug-eluting stent (DES). The following were excluded from the study: 1) patients diagnosed with diabetes mellitus, defined according to American Diabetes Association criteria.¹⁵ 2) Patients without previously known diabetes but with glycated hemoglobin A1c > 6.5% on admission. 3) Patient angiography showing in-stent restenosis. 4) Patients who used insulin or insulin sensitizer within the past 3 months.

This study was approved by the ethics committee of Qinhuangdao First Hospital, and all patients provided their written informed consent.

Biochemical Examination

Venous blood samples were collected after an overnight fast. Plasma glucose and insulin were measured as well as other parameters including cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL-C), creatinine, high-sensitivity C-reactive protein, troponin-I, and B-type natriuretic peptide. Fasting insulin (FINS) levels were measured using a double-antibody sandwich immunoassay (Elecsys 1010 analyzer, Roche Diagnostics, Mannheim, Germany). IR was assessed using the homeostasis model assessment for insulin resistance (HOMA-IR) and the following formula: $\text{HOMA-IR} (\text{mmol/L} \times \mu\text{U/mL}) = \text{fasting glucose} (\text{mmol/L}) \times \text{fasting insulin} (\mu\text{U/mL}) / 22.5$.¹⁶

Interventional Procedure

Patients were administered 300mg of aspirin and a loading dose of 300 mg clopidogrel or 180 mg ticagrelor. Coronary angiography and percutaneous coronary intervention were performed in all patients via a transradial or transfemoral approach. The angiographic findings were analyzed using a quantitative coronary angiography (QCA) system (GEQCA, CentricityAII1000–GEMnetVersion4.1.15.07). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter and lesion length were measured on diastolic frames. The SYNTAX score was calculated for each patient according to the results of coronary angiography.

Follow-Up and Study Endpoints

All patients received aspirin (100mg QD) during follow-up and clopidogrel (75mg QD) or ticagrelor (90mg BID) for at least one year. Patients underwent clinical observation for at least 24 months. Clinical follow-up was performed at 1, 6, 12, and 24 months.

The primary endpoint was major adverse cardiac events (MACE), including overall death, non-fatal MI, and target vessel revascularization (TVR). MI was diagnosed with an elevation in serum creatine kinase or troponin I three times the upper limit of normal, together with chest pain lasting more than 30 minutes.¹⁷ TVR was defined as any repeat revascularization of the stent-treated vessel.¹⁷ The secondary endpoint was angina pectoris requiring hospitalization.

Statistics Analysis

All statistical analyses were performed using SPSS17 (SPSS, Chicago, IL, USA). Continuous variables are presented as mean±standard deviation if consistent with a normal distribution; otherwise, these are presented as median and interquartile range. Categorical variables are expressed as numbers and percentages. One-way analysis of variance or the Kruskal–Wallis *H*-test was applied to analyze differences in continuous variables between groups. Categorical variables were compared with the χ^2 or Fisher's exact test.

Cox proportional hazards regression analysis was conducted to estimate the hazard ratios (HR) and their 95% confidence intervals (CI) of developing the primary endpoint. Variables with a *P* value<0.10 in the univariate analysis were included in a multivariate analysis. MACE incidence rates of 24 months were estimated using the Kaplan–Meier method. A probability value<0.05 was considered statistically significant.

Results

The enrolled patients were divided into three groups according to tertiles of FINS level (T1, low-insulin group: FINS<7.89μIU/mL; T2, medium-insulin group: 7.89μIU/mL≤FINS<14.33μIU/mL; T3, high-insulin group: FINS≥14.33μIU/mL). Patients' baseline clinical characteristics are shown in [Table 1](#). The three groups were balanced in terms of age, sex, family history, hypertension, smoking, prior MI, and clinical presentation. There were no significant differences in laboratory characteristics such as left ventricular ejection fraction (LVEF), cholesterol, TG, and LDL-C. Patients in the low-insulin group had higher HDL-C than those in the high-insulin group (*P*<0.05). BMI, waistline, HOMA-IR, and serum uric acid in the high-insulin group were higher than those in the low- and medium-insulin groups. The angiographic and procedural characteristics are shown in [Table 1](#). The target vessel showed no significant difference among the three groups. QCA analysis revealed that the high-insulin group had longer lesion length and longer stents than the low-insulin group. SYNTAX scores were higher in the high-insulin group than in the low-insulin group. Patients in the high-insulin group also had more target vessel stenosis and bifurcation lesions than those in the low-insulin group.

The baseline clinical characteristics of patients, stratified by the primary endpoint, are summarized in [Table 2](#).

Compared with the event-free group, patients with MACE had higher levels of FINS. Patients with MACE also showed higher rates of prior myocardial infarction and higher values for the HOMA-IR, BMI, creatinine, and waistline measures. As shown in [Table 2](#), patients with MACE had smaller vessel diameter, higher SYNTAX scores, and longer lesion length.

Clinical follow-up was completed in all surviving patients. Kaplan–Meier survival analyses showed that patients in the high-insulin group had an unfavorable prognosis, with higher rates of MACE and angina hospitalization than patients in the other two groups at 24 months ([Figures 1 and 2](#)). As shown in [Table 3](#), the incidence of the primary endpoint in the high-insulin group was significantly higher than that in the low-insulin group (*P*<0.05). This difference was mainly driven by the increase in TVR. However, the incidences of overall death and non-fatal MI during follow-up were similar among the FINS tertiles.

Multivariate analysis and predictors for MACE within 24 months after PCI are presented in [Table 4](#) and [Supplementary Table 1](#). As a categorical variable, hyperinsulinemia (T3, FINS≥14.33μIU/mL) showed an increased HR for the incidence of MACE (HR2.586, 95% CI 1.694–3.950; *P*=0.000) in univariate analysis. After adjustment for multiple confounders, multivariate analysis showed a similar result (HR1.870, 95% CI 1.202–2.909; *P*=0.001). Multivariate Cox regression also revealed that bifurcation lesion, small-vessel lesion, stent length, and SYNTAX score were associated with an increased HR for MACE in patients with ACS after PCI (all *P*<0.05).

Insulin level as a continuous variable was associated with an HR of 1.062 (95% CI1.025–1.010; *P*=0.001) in univariate analysis. However, in multivariate analysis, the association between insulin level and MACE was not significant after adjusting for confounding factors (HR1.036, 95% CI 0.997–1.077, *P*=0.071) ([Supplementary Table 2](#)).

Discussion

The main finding of this study is that a high insulin level was associated with an increased risk of MACE in patients with ACS and without diabetes mellitus who were undergoing PCI. Hyperinsulinemia might be a valid predictor of clinical outcomes in patients with ACS undergoing PCI.

Weakened insulin signaling or insulin resistance, together with the associated diminution in glucose

Table 1 Comparison of Clinical and Angiographic Characteristics According to FINS Status

	Low Insulin (n =157)	Medium Insulin (n =154)	High Insulin (n=157)	F or χ^2	P value
Age	62.59 ± 8.83	62.01 ± 9.15	59.21 ± 10.51	0.255	0.775
Gender (M/F)	104/53	104/50	118/39	3.444	0.179
Current smoker	77 (49.04%)	77 (50%)	76 (48.41%)	0.08	0.961
Family history	58 (36.94%)	54 (35.06%)	54 (34.39%)	0.239	0.887
Hypertension	102 (64.86%)	95 (61.68%)	101 (64.33%)	0.406	0.816
Prior MI	18 (11.46%)	11 (7.14%)	14 (8.91%)	1.761	0.415
Clinical presentation				4.337	0.362
STEMI	17	14	24		
Non-STEMI	25	30	31		
Unstable angina	115	110	102		
Grace score	74.44± 21.36	75.05± 19.23	75.21 ± 19.01	0.047	0.954
TC (mmol/L)	4.45± 1.03	4.46± 2.22	4.26 ± 1.05	0.785	0.457
TG (mmol/L)	1.72± 1.20	1.89± 1.98	2.16 ± 1.22*	2.848	0.059
LDL-C (mmol/L)	2.48 ± 0.81	2.46± 0.91	2.34 ± 0.81	1.161	0.314
HDL-C (mmol/L)	1.12± 0.24	1.06± 0.23	1.04 ± 0.22*	4.514	0.012
Glucose (mmol/L)	5.46 ± 0.78	5.42 ± 0.76	5.51 ± 0.90	0.405	0.667
HbA1c (%)	5.82 ± 0.75	5.86 ± 0.48	5.87± 0.41	0.096	0.909
Insulin (uIU/mL)	6.14± 1.41	10.68 ± 1.71**	17.69 ± 3.77***	835.16	0
HOMA-IR	1.31± 0.60	2.14± 1.06**	3.62 ± 1.93***	121.732	0
Creatinine (µmol/L)	67.89 ± 14.59	67.24 ± 15.55	75.13± 68.69	1.471	0.231
Troponin I (ng/mL) M (IQR)	0.34 (0.03–20.84)	0.35 (0.036–22.42)	0.33 (0.05–16.45)	1.198	0.549
BNP (ng/mL) M (IQR)	54.1 (22.32–145.09)	80.17 (31.5–234)	56.0 (21.07–255.4)	3.193	0.203
HCY (mmol/L)	15.84 ± 8.93	17.64 ± 9.27	16.14± 8.82	1.188	0.306
Urine (mmol/L)	332.04 ± 84.97	336.78 ± 94.19	370.56 ± 101.70*#	6.511	0.002
BMI	24.31 ± 2.82	26.25 ± 2.72**	27.84 ± 3.41***	53.53	0
Waistline (cm)	88.61 ± 11.33	92.66 ± 8.12*	94.33± 8.52**	5.811	0.003
LVD (mm)	48.93 ± 4.62	49.15 ± 4.36	49.72 ± 4.76	0.971	0.38
LAD (mm)	37.77 ± 5.49	38.25 ± 4.51	39.21 ± 7.38	1.898	0.151
LVEF (%)	65.53 ± 7.32	65.11 ± 7.13	64.19 ± 8.88	0.979	0.388
Target artery					
Left main artery	8 (5.09%)	6 (3.89%)	7 (4.45%)	0.261	0.877
Left anterior descending	95 (60.51%)	84 (54.54%)	90 (57.32%)	1.134	0.567
Left circumflex artery	22 (14.01%)	25 (16.23%)	23 (14.64%)	0.319	0.853
Right coronary artery	31 (19.76%)	31 (20.12%)	37 (23.56%)	2.626	0.269
Bifurcation	29 (18.47%)	33 (21.42%)	45 (28.66%)*	4.891	0.087
Multivessel disease	117 (74.52%)	119 (77.27%)	124 (78.98%)	0.895	0.639
Target lesion					
Reference diameter (mm)	2.91 ± 0.43	2.93 ± 0.49	3.01 ± 0.58	2.55	0.079
Lesion length (mm)	19.60 ± 8.54	20.36 ± 8.28	22.52 ± 9.39*	4.69	0.01
Diameter stenosis (%)	89.19± 10.76	90.70 ± 7.72	91.75 ± 0.63*	3.24	0.04
Syntax Score	10.81±4.21	10.73±3.97	12.79±5.03*#	10.727	0
Characteristics of DES					
Diameter (mm)	2.91 ± 0.41	2.98 ± 0.42	3.01±0.41	2.121	0.146
Length (mm)	24.26± 14.71	25.71 ± 13.09	28.87±12.24*	4.561	0.011

Notes: *P<0.05 compared with low insulin group; **P<0.01 compared with low insulin group; #P<0.05 compared with medium insulin group; ##P<0.01 compared with medium insulin group.

Abbreviations: FINS, fasting insulin; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left atrial diameter; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; TC, cholesterol; TG, Triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide.; BMI, body mass index; HCY, Homocysteine; HOMA-IR, homeostasis model assessment for insulin resistance; DES, drug-eluting stent.

Table 2 Clinical and Angiographic Characteristics of MACE and Non-MACE Group

	MACE Group (n =86)	Non-MACE (n =382)	F or χ^2	P value
Age	62.04 ± 9.44	61.14 ± 9.64	0.733	0.464
Gender (M/F)	24/62	62/320	0.017	0.896
Current smoker	46 (53.48%)	184 (48.16%)	2.830	0.093
Family history	25 (29.06%)	141 (36.91%)	0.239	0.887
Hypertension	54 (62.79%)	250 (65.44%)	0.278	0.598
Prior MI	19 (22.09)	24 (6.28%)	21.03	0.000
Clinical presentation			0.780	0.677
STEMI	11	44		
Non-STEMI	13	73		
Unstable angina	62	265		
Grace score	74.11 ± 14.78	76.84 ± 14.24	0.047	0.954
TC (mmol/L)	4.18 ± 0.95	4.43 ± 1.61	1.230	0.219
TG (mmol/L)	1.90 ± 1.02	1.93 ± 1.59	0.139	0.890
LDL-C (mmol/L)	2.37 ± 0.73	2.43 ± 0.86	0.616	0.539
HDL-C (mmol/L)	1.05 ± 0.18	1.08 ± 0.24	1.146	0.253
Glucose (mmol/L)	5.52 ± 0.66	5.45 ± 0.84	0.635	0.526
HbA1c (%)	5.77 ± 0.52	5.86 ± 0.58	0.096	0.909
Insulin (uIU/mL)	13.21 ± 4.15	11.09 ± 5.10	3.305	0.001
HOMA-IR	2.61 ± 0.95	2.30 ± 1.05	2.458	0.014
Creatinine (μmol/L)	81.59 ± 11.59	67.57 ± 15.24	2.607	0.009
Troponin I (ng/mL) M (IQR)	0.42 (0.06–33.30)	0.34 (0.03–30)	1.346	0.178
BNP (ng/mL) M (IQR)	78.01 (22.10–258.14)	46.39 (22.77–145.09)	1.405	0.160
HCY (mmol/L)	18.11 ± 11.33	16.15 ± 8.41	1.476	0.141
Urine (mmol/L)	344.81 ± 106.27	346.43 ± 92.47	0.129	0.898
BMI	26.42 ± 4.15	25.98 ± 3.25	2.520	0.012
Waistline (cm)	85.10 ± 10.69	79.01 ± 13.36	5.811	0.003
LVD (mm)	49.74 ± 4.91	49.16 ± 4.51	0.932	0.352
LAD (mm)	37.41 ± 3.84	38.58 ± 6.20	1.438	0.151
LVEF (%)	63.59 ± 9.28	65.25 ± 7.43	0.979	0.388
Target artery				
Left main artery	7 (8.13%)	14 (3.66%)	3.279	0.070
Left anterior descending	54 (62.79%)	215 (56.28%)	1.216	0.270
Left circumflex artery	11 (11.62%)	59 (15.44%)	0.389	0.533
Right coronary artery	14 (16.27%)	93 (24.34%)	2.590	0.108
Bifurcation	35 (40.69%)	72 (18.84%)	19.002	0.000
Multivessel disease	68 (79.06%)	294 (76.96%)	0.178	0.673
Target lesion				
Reference diameter (mm)	2.82 ± 0.41	2.94 ± 0.45	2.608	0.009
Lesion length (mm)	24.31 ± 9.06	20.06 ± 8.60	4.070	0.000
Diameter stenosis (%)	92.68 ± 6.07	90.07 ± 9.43	2.457	0.014
Small vessel (diameter < 2.75mm)	47 (54.65%)	59 (15.44%)	56.591	0.000
Syntax Score	14.11 ± 4.78	10.84 ± 4.24	6.292	0.000
The characteristics of DES				
Diameter (mm)	2.93 ± 0.39	2.97 ± 0.42	2.455	0.015
Length (mm)	31.15 ± 12.33	25.24 ± 13.46	3.666	0.000

Abbreviations: MACE, major adverse cardiac events; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left atrial diameter; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; TC, cholesterol; TG, Triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; BMI, body mass index; HCY, Homocysteine; HOMA-IR, homeostasis model assessment for insulin resistance; DES, drug-eluting stent.

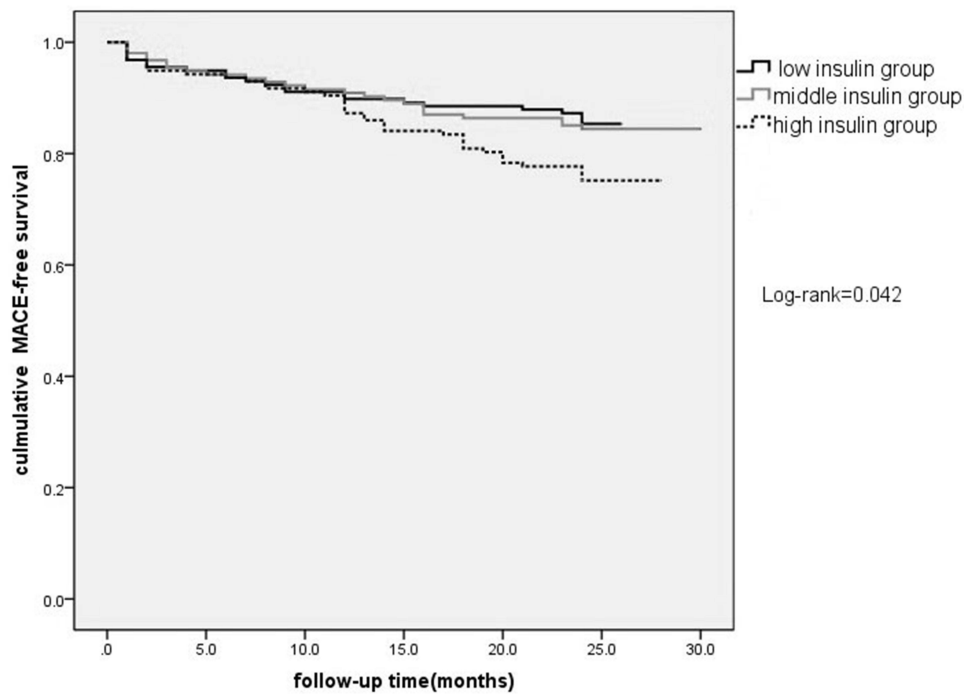


Figure 1 Comparison of MACE-free survival among different insulin groups.

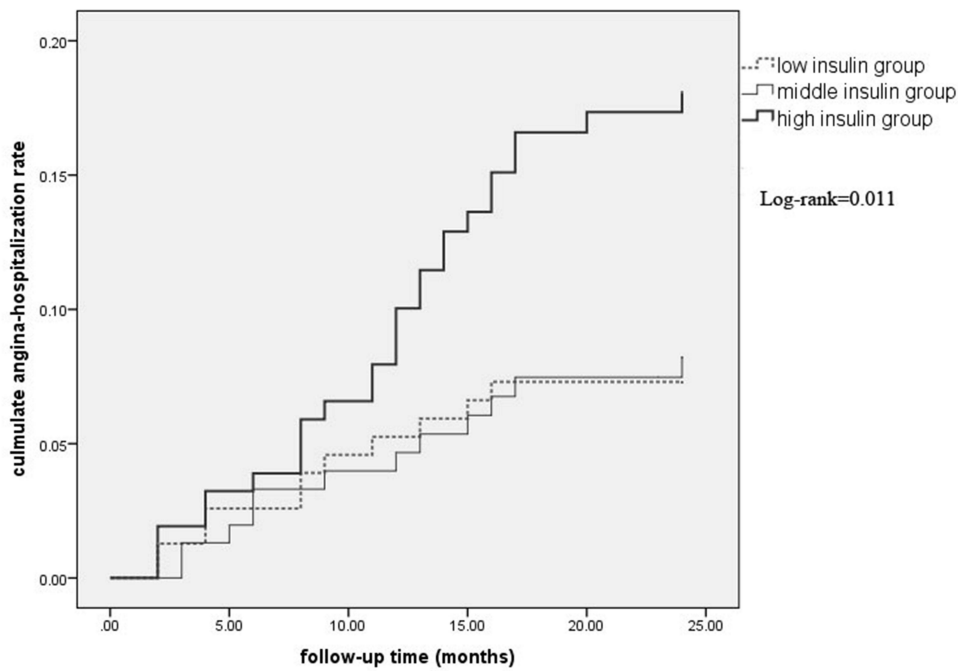


Figure 2 Comparison of angina-hospitalization among different insulin groups.

transport, promotes a compensatory increase of insulin that results in hyperinsulinemia.¹⁸ It is known that insulin has a double-phase effect on atherogenesis. Under physiological conditions, insulin stimulates the uptake of glucose and maintains glucose homeostasis.¹⁹ However, at hyper-

physiological concentrations, insulin stimulates the proliferation of vascular smooth muscle cells and triggers inflammation.²⁰ Clinical and experimental evidence suggests that hyperinsulinemia can promote obesity and endothelial dysfunction.^{21,22}

Table 3 Comparison of Clinical Outcomes After Primary PCI During 24-Month Follow-Up According to FINS Status

	Low Insulin n=157	Medium Insulin n=154	High Insulin n=157	χ^2	P
Primary endpoint					
All-cause MACE	23 (22.29%)	24 (23.37%)	39 (34.39%)*#	6.935	0.031
Death	8 (5.09%)	7 (4.54%)	7 (4.45%)	1.134	0.567
Non-fatal MI	7 (4.45%)	9 (5.84%)	10 (6.36%)	0.319	0.853
TVR	8 (5.09%)	8 (5.19%)	22 (14.01%)*#	10.999	0.004
Second endpoint					
Angina-hospitalization	13 (8.28%)	12 (7.79%)	25 (15.92%)*#	6.177	0.046

Notes: *Compared with low-insulin group, $P < 0.05$. #Compared with medium-insulin group, $P < 0.05$.

Abbreviations: FINS, fasting insulin; MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target vessel revascularization.

In the current study, we found that patients with hyperinsulinemia but without diabetes had an increased rate of MACE after undergoing PCI. As far as we know, this is the first study to discuss the direct impact of hyperinsulinemia on clinical outcomes of PCI. Our findings showed that the incidence of MACE was mainly driven by the increase in TVR. Results of multivariate analysis showed that hyperinsulinemia (as a categorical variable), but not the HOMA index, was an independent risk factor of MACE. IR is usually measured using the HOMA index, which takes into account both fasting glycemia and insulin level. Several studies have indicated that increased HOMA level is an important prognostic indicator in patients who have undergone PCI.^{23,24} However, these studies included patients both with and without diabetes mellitus. In patients without diabetes who

underwent PCI, the value of the HOMA index in predicting clinical outcomes remains controversial. Yun et al analyzed 98 consecutive patients without diabetes who underwent elective coronary angioplasty and revealed that IR (HOMA index ≥ 2.6) was an independent predictor of in-hospital and 30-day MACE rates.²⁵ Hwang et al evaluated 1-year outcomes in 229 consecutive patients with CAD and without diabetes who were treated with DES. The results showed that despite a worsening trend in angiographic outcomes in the IR group (HOMA index ≥ 2.5), this did not translate into worse 1-year major clinical outcomes following PCI with DES, as compared to the non-IR group.²⁶ Based on previous research and the current research results, hyperinsulinemia may be a more valuable predictor than the HOMA index in patients without diabetes.

Table 4 Cox Proportional Hazards Model Regression of Major Adverse Events in Patients Undergoing PCI with ACS

	Univariate Analysis		Multiple Analysis	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Bifurcation	4.428 (2.681–7.313)	0	3.394 (2.033–5.667)	0
Syntax score	1.119 (1.079–1.16)	0	1.084 (1.039–1.130)	0.001
Stent length	1.028 (1.013–1.043)	0.011	1.017 (1.002–1.032)	0.03
Stent diameter	0.791 (0.489–1.281)	0.341	–	–
Small vessel	1.609 (1.053–2.461)	0.028	1.713 (1.111–2.642)	0.015
HOMA	1.113 (0.980–1.265)	0.099	0.980 (0.825–1.093)	0.473
Hyperinsulinemia	2.586 (1.694–3.950)	0	1.870 (1.202–2.909)	0.006
BMI	1.034 (0.971–1.101)	0.297	–	–
Waist line	1.006 (0.997–1.016)	0.205	–	–
Multivessel disease	1.765 (0.978–3.185)	0.059	1.051 (0.559–1.978)	0.877
Age	1.014 (0.991–1.037)	0.246	–	–
Hypertension	0.897 (0.579–1.389)	0.627	–	–
Smoke	1.533 (0.936–2.511)	0.09	1.386 (0.888–2.163)	0.15
Prior MI	0.783 (0.480–1.277)	0.321	–	–
LDL-C	0.918 (0.690–1.222)	0.559	–	–

Abbreviations: PCI, percutaneous coronary intervention; ACS, acute myocardial syndrome; MI, myocardial infarction; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; HOMA, homeostasis model assessment; CI, confidence interval.

Although the mechanism underlying the association of hyperinsulinemia with adverse cardiovascular outcomes has not been elucidated, it may be linked to chronic inflammation and endothelial dysfunction. Hyperinsulinemia triggers oxidative stress and inflammation in macrophages and endothelial cells.²⁷ These cells produce pro-inflammatory cytokines and interleukins that contribute to vascular endothelial damage.²⁸ In this study, we also found that patients with hyperinsulinemia had more frequent angina hospitalization than patients with low and medium insulin levels. The mechanism of angina may be impaired microcirculation. Impaired coronary microcirculation is frequently observed in patients with IR and type 2 diabetes mellitus.²⁹ This impairment is driven by reduced levels of bioavailable NO. Our previous study demonstrated that hyperinsulinemia impairs endothelial progenitor cell function by down regulation of the PI-3K/Akt/eNOS pathway.¹⁰ NO is a key regulator in modulating endothelial function. Impaired NO reproduction may explain the results of the current study.

Limitations

This study has several limitations. First, this was a single-center study, and the sample size was relatively small. Second, this was a retrospective study and not a randomized controlled study; therefore, selection bias may be present. The third limitation is the relatively short duration (24 months) of follow-up. This may be a limiting factor in evaluating important clinical effects of hyperinsulinemia. Further investigation is necessary to clarify the impact of insulin among patients undergoing PCI.

Conclusions

In this study, we found an association between higher insulin levels and increased risk of MACE in patients with ACS who did not have diabetes. Hyperinsulinemia might be a valid predictor of clinical outcomes in patients with ACS and without diabetes who underwent PCI.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was approved by ethics committee of Qinhuangdao first Hospital, Hebei Medical University. And all patients provided their written informed consent.

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Disclosure

The authors declare that they have no competing interests.

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