Impact of Hyperinsulinemia on Long-Term Clinical Outcomes of Percutaneous Coronary Intervention in Non-Diabetes Patients With Acute Myocardial Syndrome.

Qiang Tan (✉ qhdtanqiang@aliyun.com)
qinhuangdao first hospital  https://orcid.org/0000-0003-1621-4428
Chen Ming
First Hospital of Qinhuangdao
Hao Jia
first hospital of Qinhuangdao
Wang Qian
First Hospital of Qinhuangdao
Sun Limin
First Hospital of Qinhuangdao
Wei Kun
qinhuandao first hospital

Original investigation

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

DOI: https://doi.org/10.21203/rs.3.rs-409639/v1

License: ☕️  This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

**Background and Objectives:** Hyperinsulinemia plays a key role in 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 with acute myocardial syndrome.

**Methods:** Between March 2016 and January 2019, patients of ACS without diabetes mellitus and received primary PCI were enrolled. 368 patients were divided into low insulin group (n=157), medium insulin group (n=154) and high insulin group (n=157) according to tertiles of fasting insulin (FINS) level. The primary endpoint was major adverse cardiac events (MACE; all-cause death, non-fatal myocardial infarction, target vessel revascularization (TVR)) at 24 months. Second endpoint was angina-hospitalization.

**Results:** High insulin group had an unfavorable prognosis, with higher rate of MACE (34.39%) compared with 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 of TVR. High insulin group also had higher rate of angina-hospitalization than low insulin group. Multivariate logistic regression showed that high insulin level (OR2.636, 95%CI 1.378-5.023), small vessel lesion (OR2.636, 95%CI 1.378-5.023), bifurcation lesion (OR3.506, 95%CI 1.048-11.922) and Syntax score(OR1.116, 95%CI 1.054-1.182) were independent predictors of MACE in ACS patients after PCI

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

Introduction

Metabolic syndrome (MetS) has a high prevalence around the world [1]. MetS is associated with the development of coronary atherosclerosis, plaque instability, and cardiovascular events in patients with or without type 2 diabetes [2–3]. The cores of metabolic syndrome are insulin resistance (IR) and hyperinsulinemia [4]. A new concept of selective insulin resistance indicates that tissues become resistant to insulin's effect on glucose transport but remain sensitive to its lipogenic effect [5]. IR may be compensatory in the body's response to prevent the metabolic syndrome. Hyperinsulinemia is more common than IR and may play a primary role in development of cardiovascular impairment in patients with MetS [6].

Our previous study demonstrated that hyperinsulinemia impaired functions of endothelial progenitor cells, which play a key role in maintaining endothelial function and vascular repairmen [7]. Other studies also indicated that hyperinsulinemia interfered with arteriolar vasodilation and NO bioavailability in obese, insulin resistant and healthy subjects [4, 8].
However, the impact of hyperinsulinemia on major clinical outcomes following percutaneous coronary intervention (PCI) is largely unknown. The aim of this study is to evaluate the impact of hyperinsulinemia on major clinical outcomes in patients with acute myocardial syndrome (ACS) undergoing PCI.

**Methods**

**Study population**

Between March 2016 and January 2019, patients with acute myocardial syndrome and received PCI were retrospectively enrolled. The including criteria is as following: 1. Patients of at least 18 years of age, who had ACS. ACS was defined as ST segment elevated myocardial infarction (STMI), non-ST segment elevated myocardial infarction and unstable angina (UA) [9]. 2. Patients received primary PCI with drug-eluting stent (DES). The following conditions were excluded from the study: 1. Patients who were diagnosed with diabetes. Diabetes mellitus was defined according to the American Diabetes Association criteria [10]; 2. Patients without previously known diabetes but with glycated hemoglobin A1c (HbA1c) >6.5% on admission; 3. Angiography showed in-stent restenosis; 4. Insulin or insulin sensitizer users. This study was approved by the ethics committee of Qinhuangdao First Hospital and all patients provided written informed consent.

**Interventional procedure**

Patients were administered 300 mg of aspirin and a loading dose of 300 mg Clopidogrel or 180mg Ticagrelor. Coronary angiography and percutaneous coronary intervention were performed in all patients by transradial or transfemoral approach. The angiographic findings were analyzed by quantitative coronary angiography (QCA) system (GE QCA, Centricity AI 1000 – GE Mnet Version 4.1.15.07). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter (MLD), lesion length were measured in diastolic frames. The Syntax score of each patient was calculated according to the results of coronary angiography.

**Follow-up and study endpoints**

All patients received aspirin (100 mg QD) and Clopidogrel (75 mg QD) or Ticagrelor (90mg BID). Patients underwent clinical observation for at least 36 months. Clinical follow up was performed at one month, six months, 12 months, 24 months.

The primary endpoint was major adverse cardiac events (MACE), including overall death, non-fatal myocardial infarction (MI), target vessel revascularization (TVR). MI was diagnosed by an elevation of serum creatine kinase or troponin three times the upper limit of normal, together with chest pain lasting more than 30 minutes [11]. TVR was defined as any repeat revascularisation of the stent treated vessel [11].

The second endpoint was angina pectoris requiring hospitalization.
Statistics analysis

All statistics analyses were performed by SPSS 17 (SPSS, Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation of the mean, and were compared by use of the one-way Anova test; The data of non normal distribution are transformed by logarithm. Categorical variables were compared with the $\chi^2$ statistics or Fisher exact test. Multivariate logistic regression was used to estimate the predictors of MACE. MACE incidence rates of two year adverse cardiac events were estimated by the Kaplan-Meier method. A probability value < 0.05 was considered statistically significant. A probability value <0.05 was considered statistically significant.

Results

The enrolled patients were divided into three groups according to tertile of fasting insulin (FINS) level (low insulin group, FINS < 7.89µIU/mL; medium insulin group, 7.89µIU/mL ≤ FINS < 14.33µIU/mL; high insulin group, FINS ≥ 14.33µIU/mL). Baseline clinical characteristics were shown in Table 1. The three groups were balanced in age, gender, family history, hypertension, smoking, prior myocardial infarction and clinical presentation. There were no significant differences in laboratory characteristics such as left ventricular ejection fraction (LVEF), cholesterol, triglyceride, low density lipoprotein-cholesterol . Low insulin group had higher high density lipoprotein than high insulin group ($P< 0.05$). BMI, waistline, HOMA-IR and serum Urine in high insulin group were higher than that in low insulin group and medium insulin group. The angiographic and procedural characteristics were shown in Table 2. The target vessel had no significant difference among the three groups. QCA analysis revealed that high insulin group had longer lesion length and longer stents than low insulin group. Syntax scores were higher in high insulin group than that in low insulin group. High insulin group also had more target vessel stenosis and bifurcation lesions than low insulin group.
Table 1
Comparison of clinical characteristics according to FINS status

|                          | Low insulin (n = 157) | Middle insulin (n = 154) | High insulin (n = 157) | F or $\chi^2$ | 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%)            | 0.080         | 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    | 17                    | 14                       | 24                    | 4.337         | 0.362   |
| STEMI                    | 25                    | 30                       | 31                    | 0.047         | 0.954   |
| Non-STEMI                | 115                   | 110                      | 102                   | 0.785         | 0.457   |
| Unstable angina          | 74.44 ± 21.36         | 75.05 ± 19.23            | 75.21 ± 19.01         | 2.848         | 0.059   |
| Grace score              | 4.45 ± 1.03           | 4.46 ± 2.22              | 4.26 ± 1.05           | 1.161         | 0.314   |
| TC (mmol/L) TG (mmol/L)  | 1.72 ± 1.20           | 1.89 ± 1.98              | 2.16 ± 1.22*          | 4.514         | 0.012   |
| LDL-C (mmol/L)           | 2.48 ± 0.81           | 2.46 ± 0.91              | 2.34 ± 0.81           | 0.405         | 0.667   |
| HDL-C (mmol/L)           | 1.12 ± 0.24           | 1.06 ± 0.23              | 1.04 ± 0.22*          | 0.096         | 0.909   |
| Glucose (mmol/L)         | 5.46 ± 0.78           | 5.42 ± 0.76              | 5.51 ± 0.90           | 835.16        | 0.000   |
| HbA1c(%)                 | 5.82 ± 0.75           | 5.86 ± 0.48              | 5.87 ± 0.41           | 121.732       | 0.000   |
| Insulin(uIU/mL)          | 6.14 ± 1.41           | 10.68 ± 1.71*            | 17.69 ± 3.77**##      | 1.471         | 0.231   |
| HOMA-IR                  | 1.31 ± 0.60           | 2.14 ± 1.06**            | 3.62 ± 1.93**##       | 1.652         | 0.194   |
| creatinine(µmol/L)       | 67.89 ± 14.59         | 67.24 ± 15.55            | 75.13 ± 68.69         | 0.879         | 0.416   |
| Lg Troponin I            | 1.34 ± 0.31           | 1.27 ± 0.39              | 1.36 ± 0.32           | 1.188         | 0.306   |
| Lg BNP                   | 1.15 ± 0.79           | 1.27 ± 0.39              | 1.54 ± 1.03           | 6.511         | 0.002   |
| HCY(mmol/L)              | 15.84 ± 8.93          | 17.64 ± 9.27             | 17.69 ± 8.82          | 53.53         | 0.000   |
| Urine(mmol/L)            | 332.04 ± 84.97        | 336.78 ± 94.19           | 370.56 ± 101.70*#     | 5.811         | 0.003   |
| BMI                      | 24.31 ± 2.82          | 27.84 ± 3.41**           | 27.84 ± 3.41***       | 0.971         | 0.380   |

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.
| LAD(mm) | Low insulin (n = 157) | Middle insulin (n = 154) | High insulin (n = 157) | F or χ² | P value |
|---------|-----------------------|--------------------------|------------------------|---------|---------|
|         | 37.77 ± 5.49          | 39.21 ± 7.38             |                        |         |         |
| LVEF(%) | 65.53 ± 7.32          | 64.19 ± 8.88             |                        |         |         |
|         | 26.25 ± 2.72**        | 92.66 ± 8.12*            |                        | 1.898   | 0.151   |
|         |                      | 49.15 ± 4.36             |                        | 0.979   | 0.388   |
|         |                      | 38.25 ± 4.51             |                        |         |         |
|         |                      | 65.11 ± 7.13             |                        |         |         |

FINS, fasting insulin; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left arterial 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.
Table 2
Comparison of angiographic and procedural characteristics according to FINS status

|                     | Low insulin n = 157 | Middle insulin n = 154 | High insulin n = 157 | F or χ² | P      |
|---------------------|---------------------|------------------------|----------------------|---------|--------|
| **Target artery**   |                     |                        |                      |         |        |
| Left main artery    | 8(5.09%)            | 6(3.89%)               | 7(4.45%)             | 0.261   | 0.877  |
| Left anterior       | 95(60.51%)          | 84(54.54%)             | 90(57.32%)           | 1.134   | 0.567  |
| descending artery   | 22(14.01%)          | 25(16.23%)             | 23(14.64%)           | 0.319   | 0.853  |
| Left circumflex      | 31(19.76%)          | 31(20.12%)             | 37(23.56%)           | 2.626   | 0.269  |
| artery              | 29 (18.47%)         | 33(21.42%)             | 45(28.66%)*          | 4.891   | 0.087  |
| Right coronary       | 117(74.52%)         | 119(77.27%)            | 124(78.98%)          | 0.895   | 0.639  |
| artery              | 2.91 ± 0.43         | 2.93 ± 0.49            | 3.01 ± 0.58          | 2.550   | 0.079  |
| **Bifurcation**     |                     |                        |                      |         |        |
|                      | 19.60 ± 8.54        | 20.36 ± 8.28           | 22.52 ± 9.39*        | 4.690   | 0.010  |
| **Multivessel**     | 89.19 ± 10.76       | 90.70 ± 7.72           | 91.75 ± 0.63*        | 3.240   | 0.040  |
| disease             |                     |                        |                      |         |        |
| **Target lesion**   | 10.81 ± 4.21        | 10.73 ± 3.97           | 12.79 ± 5.03*#       | 10.727  | 0.000  |
| Reference diameter  | 2.91 ± 0.41         | 2.98 ± 0.42            | 3.01 ± 0.41          | 2.121   | 0.146  |
| (mm)                |                     |                        |                      |         |        |
| Lesion length (mm)  | 24.26 ± 14.71       | 25.71 ± 13.09          | 28.87 ± 12.24*       | 4.561   | 0.011  |

Diameter stenosis (%)

**Syntax Score**

The characteristics of DES

Diameter(mm)

Length(mm)

FINS, fasting insulin; DES: drug-eluting stent.

The baseline clinical characteristics of the patients stratified by the primary endpoint are summarized in Table 3. Compared with event-free group, patients with MACE had higher levels of FINS. Patients with MACE also showed higher rates of prior myocardial infarction, higher level of HOMA-IR, BMI, creatinine and waistline. As shown in Table 4, patients with MACE had smaller vessel diameter. At the mean while, patients with MACE showed higher Syntax scores and longer lesion length.
### Table 3
Clinical characteristics of MACE and non-MACE group

|                      | MACE group (n = 86) | Non-MACE (n = 382) | F or χ² | 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| 11                  | 44                 | 0.780  | 0.677  |
| STEMI                | 13                  | 73                 | 0.047  | 0.954  |
| Non-STEMI            | 62                  | 265                | 1.230  | 0.219  |
| Unstable angina      | 74.11 ± 14.78       | 76.84 ± 14.24      | 0.139  | 0.890  |
| Grace score          | 4.18 ± 0.95         | 4.43 ± 1.61        | 0.616  | 0.539  |
| TC (mmol/L) TG (mmol/L) | 1.90 ± 1.02     | 1.93 ± 1.59        | 1.146  | 0.253  |
| LDL-C (mmol/L)       | 2.37 ± 0.73         | 2.43 ± 0.86        | 0.635  | 0.526  |
| HDL-C (mmol/L)       | 1.05 ± 0.18         | 1.08 ± 0.24        | 0.096  | 0.909  |
| Glucose (mmol/L)     | 5.52 ± 0.66         | 5.45 ± 0.84        | 3.305  | 0.001  |
| HbA1c(%)             | 5.77 ± 0.52         | 5.86 ± 0.58        | 2.458  | 0.014  |
| Insulin(uIU/mL)      | 13.21 ± 4.15        | 11.09 ± 5.10       | 2.607  | 0.009  |
| HOMA-IR              | 2.61 ± 0.95         | 2.30 ± 1.05        | 1.652  | 0.194  |
| creatinine(µmol/L)   | 81.59 ± 11.59       | 67.57 ± 15.24      | 0.879  | 0.416  |
| Lg Troponin I        | 1.31 ± 0.36         | 1.32 ± 0.34        | 1.476  | 0.141  |
| Lg BNP               | 1.12 ± 0.63         | 1.22 ± 0.67        | 0.129  | 0.898  |
| HCY(mmol/L)          | 18.11 ± 11.33       | 16.15 ± 8.41       | 2.520  | 0.012  |
| Urine(mmol/L)        | 344.81 ± 106.27     | 346.43 ± 92.47     | 5.811  | 0.003  |
| BMI                  | 26.42 ± 4.15        | 25.98 ± 3.25       | 0.932  | 0.352  |

MACE: major adverse cardiac events; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left arterial 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.
|                          | MACE group (n = 86) | Non-MACE group (n = 382) | F or \( \chi^2 \) | P value |
|--------------------------|---------------------|--------------------------|---------------------|---------|
| Waistline (cm)           | 85.10 ± 10.69       | 79.01 ± 13.36            | 1.438               | 0.151   |
| LVD (mm)                 | 49.74 ± 4.91        | 49.16 ± 4.51             | 0.979               | 0.388   |
| LAD (mm)                 | 37.41 ± 3.84        | 38.58 ± 6.20             | 0.151               |         |
| LVEF (%)                 | 63.59 ± 9.28        | 65.25 ± 7.43             | 0.388               |         |

MACE: major adverse cardiac events; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left arterial 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.

**Table 4**

Angiographic and procedural characteristics of MACE and non-MACE group

|                          | MACE group (n = 86) | Non-MACE group (n = 382) | F or \( \chi^2 \) | P     |
|--------------------------|---------------------|--------------------------|---------------------|-------|
| **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**          |                     |                          |                     |       |
| 68(79.06%)               | 294(76.96%)         | 19.002                   | 0.673               |       |
| **Multivessel disease**  | 2.82 ± 0.41         | 2.94 ± 0.45              | 2.608               | 0.009 |
| **Target lesion**        | 24.31 ± 9.06        | 20.06 ± 8.60             | 4.070               | 0.000 |
| Reference diameter (mm)  | 92.68 ± 6.07        | 90.07 ± 9.43             | 2.457               | 0.014 |
| Lesion length (mm)       | 47(54.65%)          | 59(15.44%)               | 56.591               | 0.000 |
| Diameter stenosis (%)    | 14.11 ± 4.78        | 10.84 ± 4.24             | 6.292               | 0.000 |
| Small vessel (diameter < 2.75mm) | 2.93 ± 0.39          | 2.97 ± 0.42            | 2.455               | 0.015 |
| **Syntax Score**         | 31.15 ± 12.33       | 25.24 ± 13.46            | 3.666               | 0.000 |

The characteristics of DES

|                          |                     |                          |                     |       |
| Diameter(mm)             |                     |                          |                     |       |
| Length(mm)               |                     |                          |                     |       |

MACE: major adverse cardiac events; DES: drug-eluting stent.
Clinical follow-up was completed in all survival patients. Kaplan-meier survival analyses showed that the high insulin group had an unfavorable prognosis, with higher rates of MACE and angina hospitalization compared with the other two groups at 24 months (Fig. 1 and Fig. 2). As shown in Table 5, the incidence of the primary endpoint in high insulin group was significantly higher than that in low insulin group ($P < 0.05$). This difference was mainly driven by the increase in target vessel revascularization. However, the incidence of overall death, non-fatal MI during follow-up were similar among the FINS tertiles.

**Table 5**
Comparison of clinical outcomes after primary PCI during 24 months’ follow-up according to FINS status.

|                  | Low insulin n = 157 | Middle insulin n = 154 | High insulin n = 157 | $\chi^2$ | $P$   |
|------------------|---------------------|------------------------|----------------------|----------|-------|
| **Primary endpoint** |                     |                        |                      |          |       |
| All-cause MACE   | 23(22.29%)          | 24(23.37%)             | 39(34.39%)*#         | 6.935    | 0.031 |
| death            | 7(4.45%)            | 9(5.84%)               | 10(6.36%)            | 0.319    | 0.853 |
| non-fatal MI     | 8(5.09%)            | 8(5.19%)               | 22(14.01%)*#         | 10.999   | 0.004 |
| TVR              | 13(8.28%)           | 12(7.79%)              | 25(15.92%)*#         | 6.177    | 0.046 |

**Second endpoint**

Angina-hospitalization

FINS, fasting insulin; MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target vessel revascularization; * compared with low insulin group, $P < 0.05$; # compared with middle insulin group, $P < 0.05$.

Multivariate analyses and predictors for MACE within 24 months after PCI are presented in table 6. After adjusting for confounding factors, multivariate logistic regression showed that the high insulin level, bifurcation lesion, small vessel lesion and Syntax score, were independent predictors of MACE in ACS patients after PCI (all $P < 0.05$).

**Table 6 Predictors of major adverse events in patients undergoing PCI with ACS.**

| variables                | Co-efficient | Odds ratio(95%CI) | $P$ value |
|--------------------------|--------------|------------------|-----------|
| Hyperinsulinemia         | 2.636        | 1.378-5.023      | 0.003     |
| Syntax score             | 1.116        | 1.054-1.182      | 0.000     |
| Small vessel (<2.75mm)   | 2.536        | 1.048-6.135      | 0.039     |
| bifurcation              | 5.506        | 2.543-11.922     | 0.000     |
Discussion

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

Weakened insulin signalling or insulin resistance, together with the associated diminution in glucose transport, promotes compensatory increase of insulin that results in hyperinsulinemia [12]. As we know, insulin has double-phase effect on atherogenesis. Under physiological conditions, insulin stimulates the uptake of glucose and maintains glucose homeostasis [13]. But at hyper-physiological concentration, insulin stimulates proliferation of vascular smooth muscle cells and triggers inflammation [14]. Clinical and experimental evidence suggests that hyperinsulinemia can promote obesity and endothelial dysfunction [15-16].

Some previous studies explored the impact of insulin resistance on clinical outcomes of PCI, but the results were controversial. Yun et al analyzed 98 consecutive non-diabetic patients 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 [17]. Hwang et al evaluated one year outcomes of 229 consecutive non-diabetic CAD patients treated with DES. The results found that despite worse trend in angiographic outcomes in the IR group (HOMA index ≥2.5), it was not translated into worse 1-year major clinical outcomes following PCI with DES as compared to the non-IR group [18].

The current study found that non-diabetic patients with hyperinsulinemia had increased MACE rate 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. Actually, the incidence of MACE was mainly driven by the increase of target vessel revascularization.

In this study, we also found that patients with hyperinsulinemia had more angina-hospitalization than patients with low and middle insulin level. The mechanism of angina may be impaired microcirculation. Impaired coronary microcirculation is frequently observed in patients with insulin resistance and T2DM. This impairment is driven by reduced levels of bioavailable nitric oxide. Our previous study demonstrated that hyperinsulinemia impaired endothelial progenitor cell's function by down regulation of PI-3K/Akt/eNOS pathway [7]. 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, it was a single center study, the sample size was relative small. Second, it is a retrospective but not a randomized controlled study, it may have selection bias. The third limitation was the relative short duration of 24 months of follow-up. It may be a limiting factor to evaluate important clinical effects of hyperinsulinemia. We still need more investigation and more time to testify the impact of insulin in patients undergoing PCI.
Conclusions

This study indicated an association between higher insulin levels and increased risk of MACEs in non-diabetes patients with ACS. Hyperinsulinemia might be a valid predictor of clinical outcomes in non-diabetes patients with ACS undergoing PCI.

Abbreviations

ACS: Acute coronary syndrome; BMI: Body mass index; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHF: Congestive heart failure; CI: Confidence interval; CVD: Cardiovascular disease; FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; HR: Hazard ratio; IR: Insulin resistance; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglyceride glucose.

Declarations

Acknowledgements

Authors’ contributions

All authors were involved in the conception and design of the study and in the collection, analysis, and interpretation of the data. All authors reviewed the final manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by S&T program of Hebei (201801B032) and Hebei medical technology project (20171252).

Availability of data and materials

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 commitee of Qinhuangdao first Hospital, Hebei Medical University. Given the retrospective nature of this study, the requirement for informed consent was waived.

Consent for publication

Not applicable.
Competing interests

The authors declare that they have no competing interests.

References

1. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014; 2014:943162
2. Caccamo G, Bonura F, Bonura F, Vitale G, Novo G, Evola S, et al. Insulin resistance and acute coronary syndrome. 2011; 211:672–675.
3. Grandl G and Wolfrum C. Hemostasis, endothelial stress, inflammation, and the metabolic syndrome. Seminars in Immunopathology. 2018; 40:215–224
4. Mahmoud A M, Ali M, Miranda E R, Mey JT, Blackburn B K, Haus J M, et al. Nox2 contributes to hyperinsulinemia-induced redox imbalance and impaired vascular function. Redox Biology. 2017; 13:288–300.
5. Williams KJ, Wu X. Imbalanced insulin action in chronic over nutrition: clinical harm, molecular mechanisms, and a way forward. Atherosclerosis. 2016; 247:225–82
6. Erion K A and Corkey B E. Hyperinsulinemia: a Cause of Obesity? Curr Obes Rep (2017) 6:178–186.
7. Tan Q, Li Y, Li X, Zhang SY. Hyperinsulinemia impairs functions of circulating endothelial progenitor cells. Acta Diabetol. 2019; 56 (7):785-795.
8. Solomon TP, Haus JM, Li Y, et al., Progressive hyperglycemia across the glucose tolerance continuum in older obese adults is related to skeletal muscle capillarization and nitric oxide bioavailability, J. Clin. Endocrinol. Metab. 2011; 96 (5): 1377–1384.
9. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2017; 69(5):570-591.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014; 37(Suppl. 1): S81–S90.
11. Tan Q, Wang QS, Liu DT, Zhang SY, Zhang Y, Li Y. Intravascular Ultrasound-Guided Unprotected Left Main Coronary Artery Stenting in the Elderly. Saudi medical journal. 2015; 36(5):549-53.
12. Velez M, Kohli S, Sabbah HN. Animal models of insulin resistance and heart failure. Heart Fail. Rev. 2014; 19:1–13.
13. Choi J H, Gimble J M, Vunjak-Novakovic G, Kaplan D L. Effects of Hyperinsulinemia on lipolytic function of three-dimensional adipocyte endothelial co-cultures. Tissue Eng Part C Methods.
14. Mackesy D Z and Goalstone M L. Insulin augments tumor necrosis factor-alpha stimulated expression of vascular cell adhesion molecule-1 in vascular endothelial cells. Journal of Inflammation. 2011; 8:34-38.

15. Isfort M, Stevens SC, Schaffer S, Jong CJ, Wold LE. Metabolic dysfunction in diabetic cardiomyopathy. Heart Fail. Rev. 2014; 19:35–48

16. Breen DM, Chan KK, Dhaliwall JK, et al. Insulin increases reendothelialization and inhibits cell migration and neointimal growth after arterial injury. Arterioscler Thromb Vasc Biol. 2009; 29:1060-1066.

17. Yun KH, Jeong MH, Kim KH, Hong YJ, Park HW, Kim JH, Ahn YK, Cho JG, Park JC, Kim NH, Oh SK, Jeong JW, Kang JC. The effect of insulin resistance on prognosis of non-diabetic patients who underwent percutaneous coronary intervention. J Korean Med Sci 2006;21:212–6.

18. Hwang I K, Kim Y K, Rha S W, Ra J E, Seo B S, Lee J K. Impact of insulin resistance on 1-year clinical outcomes in non-diabetic patients undergoing percutaneous coronary intervention with drug-eluting stents. Journal of Cardiology. 2013;61:113–116.