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Adropin – A new player in energy regulation predicts long-term prognosis of patients with acute myocardial infarction

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ABSTRACT

Background: As a novel energy homeostasis regulator, Adropin not only plays a vital part in meditating energy metabolism, but also has a certain correlation with atherosclerotic diseases. The purpose of this study was to evaluate the effect of Adropin on the long-term prognosis of patients with acute myocardial infarction (AMI).

Methods: 162 recruited patients with AMI were divided into low Adropin group (Adropin<166.3 pg/mL, n = 82) and high Adropin group (Adropin≥166.3 pg/mL, n = 80), according to the mean value of serum Adropin level. Patients were followed up and major adverse cardiac events (MACEs) were recorded. The Kaplan-Meier method and Cox regression model were used to evaluate the survival of patients and the related factors of cardiac events.

Results: Diabetes was more common in low Adropin group than that in high Adropin group ($P < 0.05$). Patients were followed up for an average of 50.3 ± 19.2 months. MACEs occurred in 37 patients (22.8%), including 6 cardiac deaths (3.7%), 14 recurrent myocardial infarction (8.6%) and 17 rehospitalization of heart failure (10.5%). The incidence of recurrent myocardial infarction in low Adropin group was higher than that in high Adropin group (13.4% vs 3.8%, $P < 0.05$). There was no significant difference in the overall incidence of MACE, cardiac death and rehospitalization of heart failure between the two groups. Kaplan-Meier method (log rank test) analysis results showed that patients with low Adropin had lower survival rate without recurrent myocardial infarction (log rank $P = 0.035$).

Conclusion: Low Adropin level was associated with an increased risk of long-term recurrent myocardial infarction in patients with AMI.

1. Introduction

Cardiovascular disease is the major cause of mortality in people all over the world, and it accounts for more than 40% of all deaths

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in China [1,2]. Coronary heart disease is a kind of serious cardiovascular disease, featured with coronary artery stenosis or obstruction caused by coronary atherosclerotic plaque hyperplasia [3]. If the plaque ruptures, an acute thrombus will be formed to suddenly block the coronary artery lumen, resulting in acute myocardial ischemia and hypoxia, and myocardial necrosis, which will develop into acute myocardial infarction (AMI) [4]. The morbidity and fatality of AMI are both high [5]. Although emergency intervention is considered to be the best method for the treatment of AMI now [6], the long-term prognosis and life quality of AMI patients are still not optimistic. Some biomarkers such as troponin, myoglobin and MB subtypes of creatine kinase have been gradually recognized in the diagnosis of AMI and evaluation of the prognosis, but there are still some limitations [7–9]. Troponin is currently recommended as the main biomarker for the diagnosis of AMI. Other major biomarkers include creatine kinase-MB (CK-MB) and myoglobin. Advantages of troponins over CK-MB and myoglobin include their greater sensitivity and specificity for myocardial injury, as well as their longer half-life, which allows for a longer detection window. Furthermore, troponin is less affected by skeletal muscle injury than CK-MB and myoglobin. Troponin levels may not rise until several hours after the onset of AMI symptoms, leading to delays in diagnosis and treatment. CK-MB and myoglobin have the advantage of being released into the bloodstream more quickly after myocardial injury and therefore can be detected earlier than troponin. However, CK-MB and myoglobin are less specific to myocardial injury than troponin, and are more susceptible to skeletal muscle injury and renal insufficiency. The exploration of new biomarkers and influencing factors related to AMI and other cardiovascular diseases is still a big challenge.

Adropin is a newly-discovered secretory protein, containing 76 amino acids that are related to energy homeostasis-coded regulatory peptides. It is mainly expressed in human liver, brain, vascular endothelium and cardiomyocyte etc [10,11]. Originally, Adropin is regarded as an energy metabolic factor that can regulate insulin sensitivity and energy metabolism balance in the body [12]. Adropin has been shown to play a role in regulating the energy metabolism of cardiomyocytes through multiple mechanisms. One of the key mechanisms by which adropin regulates cardiomyocyte energy metabolism is through the activation of AMP-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis. AMPK is activated upon energy depletion and leads to the stimulation of energy-producing pathways, such as glucose uptake and fatty acid oxidation, while inhibiting energy-consuming pathways, such as protein synthesis. Adropin has been shown to activate AMPK in cardiomyocytes, resulting in increased glucose uptake and fatty acid oxidation, and reduced oxidative stress and inflammation. Adropin has also been shown to regulate the expression and activity of key enzymes involved in energy metabolism, such as pyruvate dehydrogenase kinase (PDK) and carnitine palmitoyltransferase 1 (CPT1). PDK inhibits the entry of glucose-derived pyruvate into mitochondria for oxidative metabolism, while CPT1 is involved in the transport of fatty acids to mitochondria for oxidation. Adropin has been shown to decrease PDK expression and activity, leading to increased pyruvate oxidation and ATP production, while increasing CPT1 expression and activity, leading to increased fatty acid oxidation and energy production. In addition to its effects on energy metabolism, adropin has also been shown to have anti-apoptotic and anti-inflammatory effects in cardiomyocytes, which may further contribute to its cardioprotective effects [13]. Endothelial dysfunction is a critical early sign in atherosclerosis, which is essential in coronary artery disease and acute coronary syndromes. Recently, studies have shown that a decrease in serum Adropin can be a sign of coronary atherosclerosis [14], but the application of Adropin in the diagnosis and prognosis of AMI remains to be further studied.

2. Materials and methods

2.1. Study subjects

A total of 162 patients who were diagnosed with AMI and treated with emergency percutaneous coronary intervention (PCI) in the Second Affiliated Hospital of Soochow University from January 2013 to June 2017 were enrolled in the study. The definition of myocardial infarction is based on the third universal definition of myocardial infarction [15]. The exclusion criteria including (1) history of previous myocardial infarction and PCI, (2) history of trauma, major surgery or stroke within the 6 months before admission, (3) hemorrhagic disease, malignant tumors, not suitable for the use of iodine contrast agent, severe liver and renal dysfunction, (4) unwilling to participate in this study. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Soochow University.

2.2. Biochemical investigations and clinical data collection

Samples of venous blood were collected within 1 h after admission, and stored at −80 °C prior to analyses. Serum Adropin level was measured using a commercial ELISA kit (JRDUN Biotechnology Co, Ltd, Shanghai, China). The mean value of serum Adropin level in the 162 recruited patients was 166.3 ± 34.2 pg/mL. Based on the mean value of serum Adropin level, patients were divided into low Adropin group (Adropin<166.3 pg/mL, n = 82) and high Adropin group (Adropin≥166.3 pg/mL, n = 80). Troponin T, MB subtypes of creatine kinase (CKMB), N-terminal pro-brain natriuretic peptide (NT-proBNP), blood routine, fasting plasma glucose, blood urea nitrogen, creatinine, blood uric acid and serum lipidprofiles were assessed using standard methods.

The demographic and clinical characteristics of the study patients were collected from hospital case records. These included age, gender, smoking, alcohol consumption, hypertension, diabetes mellitus, stroke and blood pressure. Patients' height (m) and weight (kg) in light clothing were measured, and the body mass index (kg/m^2) was calculated.

2.3. Angiographic data collection

Coronary angiography was performed using standard techniques through radial or femoral approaches. Angiographic analysis was

carried out by two experienced interventional cardiologists who were blinded to the study. The myocardial infarction site, culprit vessel, stent implantation rate, stent number, stent diameter, stent length, preoperative thrombolysis in myocardial infarction (TIMI) blood flow grading, postoperative TIMI blood flow grading and diseased vessel number were recorded.

2.4. Follow-up and clinical outcomes

All selected patients completed follow-up. The occurrence of major adverse cardiac events (MACEs) in all patients was recorded including cardiac death, recurrent myocardial infarction and heart failure readmission. Cardiac death includes sudden death, or subjects die of heart related diseases such as myocardial infarction, heart failure or malignant arrhythmia.

2.5. Statistical analyses

The continuous variables between the two groups were compared by independent-sample *t*-test if the data were normally distributed, and Mann-Whitney *U* test if skewed. Categorical variables were expressed as frequency (percentage), and compared by the chi-square test. Kaplan Meier method (log rank test) was used to evaluate the MACEs free survival rate of patients. Cox regression was used to evaluate the independent predictors of MACEs. SPSS 26.0 for Windows (SPSS Inc., Illinois, USA) was used for all statistical analyses, and two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic, clinical and blood characteristics

Patients' demographic, clinical and blood characteristics were showed in Table 1. Diabetes was more common in low Adropin group than that in high Adropin group ($P < 0.05$). High Adropin group had higher serum Adropin level (196.2 ± 17.9 pg/mL) than that in low Adropin group (137.2 ± 16.7 pg/mL, $P < 0.001$). No significant differences in age, gender, smoking, alcohol consumption, hypertension, diabetes mellitus, stroke, blood pressure, height, weight, body mass index, left ventricular ejection fraction (LVEF), length of hospitalization, white blood cell, red blood cell, platelet, fasting blood glucose, cholesterol, triglyceride, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), blood urea nitrogen, creatinine, blood uric acid, Troponin T peak, CKMB peak and NT-proBNP were observed between the two groups.

Table 1
Demographic and clinical characteristics.

Characteristics	Low Adropin group (n = 82)	High Adropin group (n = 80)	P value
Male (%)	69 (84.1)	61 (76.3)	0.239
Age (year)	61.5 ± 12.7	64.7 ± 11.6	0.099
Smoking (%)	49 (59.8)	47 (58.8)	0.896
Alcohol consumption (%)	18 (22.0)	12 (15.0)	0.313
Hypertension (%)	48 (58.5)	51 (63.8)	0.523
Diabetes mellitus (%)	19 (23.2)	8 (10.0)	0.034
Storke (%)	9 (11.0)	2 (2.5)	0.057
Systolic blood pressure (mmHg)	130.1 ± 20.8	126.3 ± 24.6	0.292
Diastolic blood pressure (mmHg)	75.7 ± 12.6	72.4 ± 14.3	0.120
Height (m)	1.67 ± 0.08	1.66 ± 0.07	0.453
Weight (kg)	68.0 ± 10.7	68.36 ± 8.9	0.815
Body mass index (kg/m^2)	24.1 ± 2.7	24.6 ± 2.5	0.269
LVEF (%)	53.3 ± 11.5	56.8 ± 12.2	0.197
Length of hospitalization (day)	7.6 ± 2.76	7.8 ± 5.3	0.674
White blood cell (× 10^9/L)	9.4 ± 3.2	9.0 ± 3.4	0.478
Red blood cell (× 10^{12}/L)	4.74 ± 0.67	4.70 ± 0.44	0.699
Platelet (× 10^9/L)	210.0 ± 59.6	207.2 ± 54.8	0.774
Fasting blood glucose (mmol/L)	7.1 ± 2.8	6.9 ± 3.0	0.917
Cholesterol (mmol/L)	4.69 ± 1.10	4.63 ± 1.07	0.746
Triglyceride (mmol/L)	1.34 ± 0.74	1.61 ± 1.52	0.148
LDL-C (mmol/L)	3.01 ± 1.04	2.85 ± 0.81	0.282
HDL-C (mmol/L)	1.04 ± 0.33	1.05 ± 0.28	0.901
Blood urea nitrogen (mmol/L)	5.85 ± 1.92	5.64 ± 2.68	0.533
eGFR (mL/min/1.73m^2)	100.9 ± 40.2	92.1 ± 33.5	0.135
Blood uric acid (μmol/L)	328.8 ± 93.2	348.6 ± 104.0	0.202
Troponin T (pg/mL)	4588.4 ± 3817.3	4115.4 ± 4139.6	0.496
CKMB (max) (μg/L)	191.4 ± 330.3	139.5 ± 126.8	0.250
NT-proBNP (max) (pg/mL)	2172.9 ± 4792	1605.6 ± 3911.2	0.456
Adropin (pg/mL)	137.2 ± 16.7	196.2 ± 17.9	0.000

LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CKMB, MB subtypes of creatine kinase; NT-proBNP, N-terminal pro B-type natriuretic peptide.

3.2. Angiographic characteristics and discharge medications

Patients' angiographic characteristics and discharge medications were presented in Table 2. There were no significant differences in the myocardial infarction site, culprit vessel, stent implantation rate, stent number, stent diameter, stent length, preoperative TIMI blood flow grading, postoperative TIMI blood flow grading and diseased vessel number between the two groups.

No significant differences in the discharge medications were observed between the two groups including aspirin, clopidogrel, ticagrelor, statins, ezemab, β-blockers, angiotensin converting enzyme inhibitor/angiotensin receptor antagonis, spirolactone, loop diuretics and digoxin.

4. Clinical outcomes

The study patients were followed up for an average of 50.3 ± 19.2 months. MACEs occurred in 37 patients (22.8%), including 6 cardiac death (3.7%), 14 recurrent myocardial infarction (8.6%) and 17 heart failure readmission (10.5%). The incidence of recurrent myocardial infarction in low Adropin group was higher than that in high Adropin group (13.4% vs 3.8%, $P < 0.05$). There was no significant difference in the overall incidence of MACE, cardiac death and heart failure readmission between the two groups (Table 3).

4.1. Survival analysis results

Kaplan Meier method (log rank test) was used to evaluate the survival of patients without cardiac events. The results showed that patients with low Adropin had lower survival rate without recurrent myocardial infarction (log rank $P = 0.035$) (Fig. 1). Adropin had no significant effect on the survival rate without overall MACEs (log rank $P = 0.441$), the survival rate without cardiac death (log rank $P = 0.987$) and the survival rate without heart failure readmission (log rank $P = 0.432$).

Cox regression model analyzed the survival of the subjects and the influencing factors related to the occurrence of cardiac events. Gender, BMI, age, smoking, alcohol consumption, diabetes, hypertension, stroke, lipidprofiles, renal function, fasting blood glucose, white blood cell, red blood cell, CKMB, troponin T, NT-proBNP, LVEF, infarction site, culprit vessel, diseased vessel number,

Table 2
Angiographic characteristics and discharge medications.

Characteristics	Low Adropin group (n = 82)	High Adropin group (n = 80)	P value
Myocardial infarction site (%)			0.421
Anterior	53 (64.6)	46 (57.5)	
Inferior and posterior	29 (35.4)	34 (42.5)	
Culprit vessel (%)			0.079
LAD	53 (64.6)	46 (57.5)	
LCX	13 (15.9)	7 (8.8)	
RCA	16 (19.5)	27 (33.8)	
Stent implantation (%)	76 (92.7)	72 (90.0)	0.587
Stent number	1.12 ± 0.55	1.06 ± 0.64	0.558
Stent diameter (mm)	2.99 ± 0.48	3.00 ± 0.41	0.903
Stent length (mm)	25.7 ± 13.0	26.0 ± 14.6	0.912
Preoperative TIMI blood flow grading (%)			0.919
Grade 0	55 (67.1)	53 (66.3)	
Grade 1	10 (12.2)	10 (12.5)	
Grade 2	8 (9.8)	6 (7.5)	
Grade 3	9 (11.0)	11 (13.8)	
Postoperative TIMI blood flow grading (%)			0.857
Grade 1	3 (3.7)	2 (2.5)	
Grade 2	17 (20.7)	15 (18.8)	
Grade 3	62 (75.6)	63 (78.8)	
Diseased vessel number (%)			0.819
1 vessel	30 (36.6)	33 (41.3)	
2 vessel	29 (35.4)	27 (33.8)	
3 vessel	23 (28.0)	20 (25.0)	
Discharge medications (%)			
Aspirin	82 (100)	80 (100)	1.000
Clopidogrel	44 (53.7)	41 (51.3)	0.875
Ticagrelor	38 (46.3)	39 (48.8)	0.875
Statins	81 (98.8)	79 (98.8)	1.000
Ezemab	26 (31.7)	24 (30.0)	0.866
β receptor blockers	63 (76.8)	60 (75.0)	0.855
ACEI/ARB	34 (41.5)	37 (46.3)	0.635
Spirolactone	7 (8.5)	8 (10.0)	0.792
Loop diuretics	13 (15.9)	13 (16.3)	0.945
Digoxin	1 (1.2)	1 (1.3)	0.986

LAD, left anterior descending; LCX, left Circumflex; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor antagonist.

Table 3
Incidence of MACEs.

Variables	Low Adropin group (n = 82)	High Adropin group (n = 80)	P value
Total MACEs (%)	21 (25.6)	16 (20.0)	0.456
Cardiac death (%)	3 (3.7)	3 (3.8)	0.975
Recurrent myocardial infarction (%)	11 (13.4)	3 (3.8)	0.047
heart failure readmission (%)	7 (8.5)	10 (12.5)	0.452
Follow-up time (months)	49.7 ± 19.3	50.8 ± 19.1	0.706

MACEs, major adverse cardiovascular events.

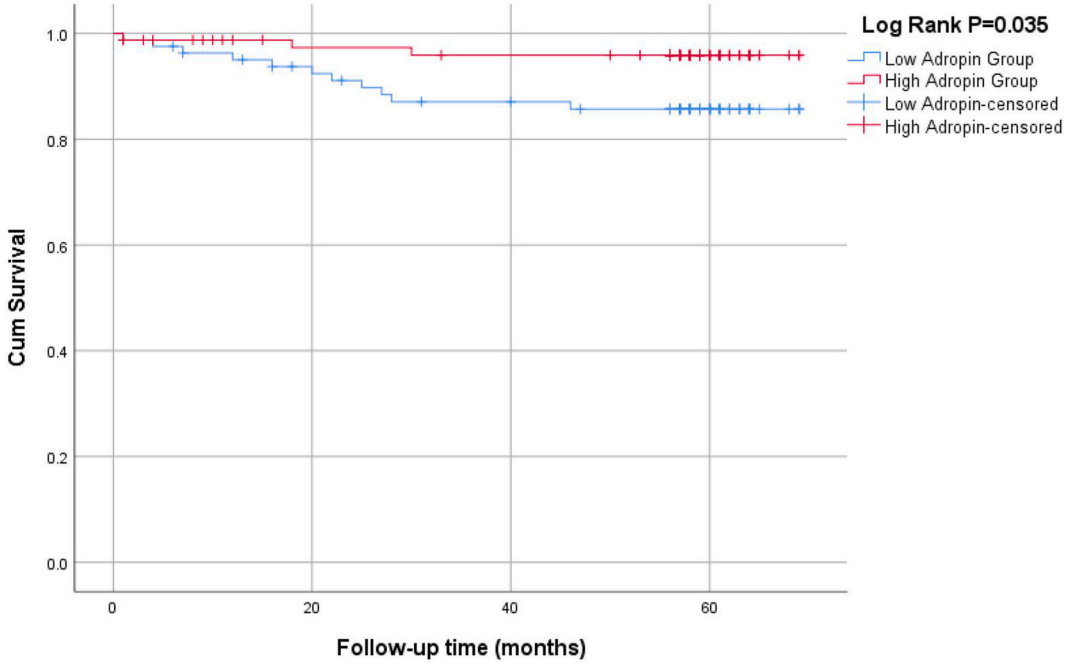

Fig. 1. Kaplan-Meier curve of Adropin on survival rate of patients without recurrent myocardial infarction.

Table 4
Cox regression analysis of MACEs occurrence, recurrent myocardial infarction and heart failure readmission.

Variable	Adjusted Odd Ratio (AOR)	95% Confidence Interval (95% CI)	P value
MACEs occurrence			
Male	6.614	1.074–30.748	0.042
Age	1.067	1.010–1.129	0.021
Diseased vessel number	2.022	1.195–3.420	0.009
HDL-C	0.243	0.061–0.958	0.043
LDL-C	1.670	0.937–2.976	0.082
Creatinine	1.017	0.990–1.045	0.210
Recurrent myocardial infarction			
Age	1.058	1.002–1.117	0.041
Diseased vessel number	4.730	1.917–11.676	0.001
HDL-C	0.121	0.024–0.606	0.015
Adropin	0.980	0.959–1.002	0.071
Heart failure readmission			
LVEF	0.502	0.312–0.810	0.005
CKMB peak	1.008	1.001–1.015	0.036
Creatinine	4.566	1.435–12.493	0.010
LDL-C	2.469	1.056–5.780	0.037

LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol. LVEF, left ventricular ejection fraction; CKMB, MB subtypes of creatine kinase.

preoperative TIMI blood flow grading, postoperative TIMI blood flow grading and Adropin level were included in the model. The results showed that male (AOR = 6.614, 95% CI = 1.074–30.748, P = 0.042), age (AOR = 1.067, 95% CI = 1.010–1.129, P = 0.021), diseased vessel number (AOR = 2.022, 95% CI = 1.195–3.420, P = 0.009) and HDL-C (AOR = 0.243, 95% CI = 0.061–0.958, P = 0.043) were independent predictors of MACEs (Table 4).

Cox regression analysis results of recurrent myocardial infarction showed that age (AOR = 1.058, 95% CI = 1.002–1.117, P = 0.041), diseased vessel number (AOR = 4.730, 95% CI = 1.917–11.676, P = 0.001), HDL-C (AOR = 0.121, 95% CI = 0.024–0.606, P = 0.015) were independent predictors of recurrent myocardial infarction. Although Adropin was not an independent risk factor for recurrent myocardial infarction, patients in the low Adropin group had an increased risk of recurrent myocardial infarction (AOR = 0.980) (Table 4).

Cox regression analysis results of heart failure readmission showed that LVEF (AOR = 0.502, 95% CI = 0.312–0.810, P = 0.005), CKMB peak (AOR = 1.008, 95% CI = 1.001–1.015, P = 0.036), creatinine (AOR = 4.566, 95% CI = 1.435–12.493, P = 0.010) and LDL-C (AOR = 2.469, 95% CI = 1.056–5.780, P = 0.037) were the independent predictors of heart failure readmission (Table 4).

5. Discussion

This study investigated the effect of new energy homeostasis regulator Adropin on the long-term prognosis of patients with AMI. The results showed that the incidence of recurrent myocardial infarction in the low Adropin group was higher than that in the high Adropin group. The survival analysis showed that the low Adropin group had a lower survival rate without recurrent myocardial infarction. It is suggested that low Adropin level is associated with an increased risk of long-term recurrent myocardial infarction in patients with AMI.

As a serious type of coronary artery disease, AMI progresses rapidly and presents to be the mainspring of global death. If not diagnosed and treated in time, AMI will seriously endanger and ruin the health and life of patients. With the continuous progress of medicine, the mortality of AMI has decreased, but the MACEs after AMI are still common and have attracted the attention of cardiologists. Moreover, due to the influence of various factors, the incidence of AMI is increasing, and more frequently-seen in young people. As a result, it is critical to identify the important markers with possible predictive value for the long-term prognosis of AMI, thus reducing the mortality and long-term complications of AMI and improving the survival rate and life quality of patients.

Under the stimulation of various inducing factors, coronary atherosclerotic plaques rupture, and its substances are released into the blood to form thrombosis, which then causes a blockage of the coronary artery, a sharp reduction or even interruption of the blood supply to the heart, and finally led to acute myocardial ischemia and necrosis [16–19]. Cardiac biomarkers have been considered as the "gold standard" for monitoring AMI. From the previous creatine kinase and CKMB to the present troponin T and troponin I, the sensitivity and specificity have been greatly improved. However, an increasing number of studies have shown that any biomarker of myocardial cell necrosis is not complete with certain limitations [20,21]. So, it is particularly important to explore new biomarkers and influencing factors related to AMI to improve the early diagnostic ability and predict the long-term prognosis.

Existed in all tissues and cells of human widely, Adropin is a newly discovered secretory regulatory protein involved in energy homeostasis and insulin response [22,23], and has an expression in the liver, the brain, endothelial cells and cardiomyocytes [11,12]. Recent studies have shown that in addition to human energy metabolism, Adropin is also closely related to cardiovascular diseases, such as coronary artery disease, hypertension and heart failure [24–28]. Zhao et al. [27] showed that the serum Adropin level of coronary artery disease patients was significantly lower in comparison with that of healthy group, and low Adropin was associated with more severe coronary atherosclerosis. Gulen et al. [28] also reported that the serum Adropin level of patients with hypertension was significantly lower than that of those with normal blood pressure. Besides, slow coronary artery blood flow is a frequent reason of recurrent chest pain in patients, with an incidence of 1–7% in patients undergoing CAG [29]. Research has found that Adropin is associated with slow coronary artery blood flow, and its level in patients with slow blood flow is significantly reduced [30].

Regarding the relationship between Adropin and AMI, Yu et al. [14] showed that the serum Adropin level of AMI patients was significantly lower than that of healthy control and stable angina pectoris group. Multiple regression analysis indicated a decreased Adropin could be an indicator of AMI occurrence. What's more, Ertem et al. [31] studied patients with non-ST segment elevation myocardial infarction, and the results showed that the serum Adropin level of patients with non-ST segment elevation myocardial infarction was also significantly lower than that of healthy control. The findings demonstrate Adropin may have a protective function in cardiovascular diseases like atherosclerosis, coronary artery disease and myocardial infarction. Herein, the long-term recurrent myocardial infarction in the low Adropin group was significantly higher, suggesting that low Adropin level was linked to a high risk of long-term myocardial infarction recurrence. Considering this, Adropin not only could predict the occurrence of myocardial infarction, but also be related to the long-term prognosis of AMI patients. Guidelines now recommend that a dose of rivaroxaban (2.5 mg twice daily) should be considered in patients with coronary artery disease who are at high risk of subsequent events and at low risk of bleeding. Patients with low Adropin levels may be considered as high ischemic risk patients, and the addition of a dose of rivaroxaban (2.5 mg twice daily) may reduce the risk of reinfarction.

Currently, the possible mechanism of Adropin protecting cardiovascular system has not been fully clarified. Endothelial dysfunction is considered to be one of the major pathological changes in the development of cardiovascular diseases. Clinically, vascular endothelial dysfunction will lead to an increased incidence of hypertension, coronary artery disease and heart failure and so on. Adropin is a peptide that plays a role in regulating insulin resistance and blood lipids. It is reported that Adropin not only regulates metabolism, but also antagonizes endothelin, up-regulates the expression of eNOS, increases the production of (NO), thus exerting a protective effect on the vascular endothelium [13,32]. Some studies have demonstrated that homocysteine and inflammatory factors are negatively correlated with serum Adropin levels, indicating that Adropin may act as an antagonistic role against the above factors,

and thus play a cardiovascular protective effect [33–35]. Also, other studies discover that high homocysteine level is linked to the onset of atherosclerosis and cardiovascular disease risk factors, because high blood homocysteine and C-reactive protein will cause vascular endothelial damage and platelet activation, further promoting the synthesis and release of inflammatory factors and accelerating the process of atherosclerosis [36,37]. Zhao et al. [33] discovered the serum Adropin level of patients with hyperhomocysteinemia was lower than that of control group, and low Adropin level had a relation to high homocysteinaemia, and independently related to more severe coronary atherosclerosis. In addition, Hu et al. [34] found that Adropin significantly decreased tumour necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) in the pancreatic tissues of diabetic rats. In the high-fat mouse model established by Akcılar et al. [35], after intraperitoneal injection of Adropin in mice, Adropin also reduced the mRNA expressions of TNF-α and IL-6 by regulating inductive eNOS to improve the isocyanine resistance and lipid metabolism of the mouse pancreas.

Herein, our study exhibited the prevalence of diabetes in the high Adropin group was significantly lower than that in the low Adropin group. This finding is related to the Adropin-mediated balance of systemic energy homeostasis and insulin sensitivity regulation. As reported by Altamimi et al. [38], Adropin can regulate the metabolism of blood glucose by increasing insulin sensitivity, stimulating glucose oxidation and inhibiting fatty acid oxidation. Zang et al. [39] presented that, comparing with subjects without diabetes, the serum Adropin of diabetic patients was significantly reduced, and Adropin was significantly negatively correlated with BMI, triglyceride, haemoglobin A1c, insulin resistance index, fasting blood glucose and high-sensitivity C-reactive protein. This indicates that Adropin may be related to the pathological process of diabetes by regulating insulin sensitivity, lipid metabolism and the inflammatory response. Moreover, Beigi et al. [40] revealed low serum Adropin had an association with the development of gestational diabetes. Li et al. [41] reported low serum Adropin not only was related to the occurrence of diabetes, but also increased the risk of diabetic retinopathy.

Furthermore, this study indicated that factors such as gender, age, the number of diseased vascular branches and blood lipid indices were associated with the occurrence of long-term MACEs, which suggested that the prognosis of AMI patients was affected by multiple factors. The treatment of AMI patients is a systematic process, including the control of risk factors, the prevention of myocardial infarction, reperfusion therapy and life-long rehabilitation treatment. Therefore, comprehensive treatment benefits to the improvement of the prognosis and life of AMI patients.

6. Limitations

The findings must be interpreted in light of the study's limitations. This is a single center study, rather than multi-center expansion study, and the reported results were based on a relatively small patient cohort. In addition, the study subjects were AMI patients undergoing emergency PCI, not all types of coronary artery disease. The effect of Adropin on the progression of coronary atherosclerosis and the prognosis of all commers with coronary artery disease are not clear. Therefore, more multi-center studies with larger sample size, wider range of patients and long-term follow-up are needed to investigate the association of Adropin with the prognosis of patients with coronary artery disease.

7. Conclusions

In conclusion, low Adropin level was associated with the increased risk of long-term recurrent myocardial infarction in AMI patients suggesting the potentially protective effect of Adropin against coronary artery disease.

Ethics statement

This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Soochow University (JD-LK-038-01). All patients provided written informed consent.

Author contribution statement

Xiansong Chang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Fulu Jin: Li Wang: Performed the experiments; Wrote the paper.

Yufeng Jiang: Peiyu Wang: Contributed reagents, materials, analysis tools or data.

Junyan Liu: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Liangping Zhao: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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