The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2019; 26: 856-867. http://doi.org/10.5551/jat.47043

Time-Dependent Change in Omentin-1 Level Correlated with Early Improvement of Myocardial Function in Patients with First Anterior ST-Segment Elevation Myocardial Infarction After Primary Percutaneous Coronary Intervention

Yong Zhu[1, 2], Chengping Hu[1, 2], Yu Du[1, 2], Jianwei Zhang[1, 2], Jinxing Liu[1, 2], Guojie Cheng[3], Hongya Han[1, 2] and Yingxin Zhao[1, 2]

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China
[2]Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing, China
[3]Beijing Da Xing Hospital, Capital Medical University, Beijing, China

Aim: Omentin-1, as a novel adipocytokine, ameliorates obesity-associated disorders and suppresses the development of atherosclerotic lesions. The present research investigated the correlation between serum omentin-1 and post-infarction myocardial function.

Methods: A total of 52 patients with first anterior ST-segment elevation myocardial infarction (STEMI) were recruited into this study. Participants were divided into two subgroups according to median admission omentin-1 concentration. $\delta 1$ was defined as (admission omentin-1 level) - (serum omentin-1 at 24 hours after admission) and $\delta 2$ was defined as (admission omentin-1 level) - (serum omentin-1 at 72 hours after admission). The change in left ventricular ejection fraction (LVEF) was regarded as (LVEF at 3 months post-STEMI)−(LVEF at 2 days post-STEMI).

Results: Admission omentin-1 level was the highest, while omentin-1 decreased over the following 3 days. The high admission omentin-1 group had lower peak muscle brain fraction of creatine kinase (CK−MB). Additionally, the change in LVEF and the global LVEF at 3 months post-STEMI all ameliorated significantly in the high admission omentin-1 group. For the time-dependent change in omentin-1, there were negative associations among $\delta 1$, $\delta 2$, and peak CK−MB. $\delta 1$ and $\delta 2$ also correlated positively with LVEF at 3 months post-STEMI. Most importantly, $\delta 1$ ($r=0.346$, $p=0.012$) and $\delta 2$ ($r=0.439$, $p=0.001$) also correlated positively with the change in LVEF. After multivariate linear regression analysis, $\delta 1$ (Beta=0.026, 95% CI 0.011 to 0.041, $p=0.001$) and $\delta 2$ (Beta=0.024, 95% CI 0.009 to 0.038, $p=0.003$) also remained associated with the change in LVEF.

Conclusions: The admission omentin-1 and time-dependent change in omentin-1 level all have a significant correlation with the early improvement of post-infarction myocardial function. While only the time-dependent change in omentin-1 ($\delta 1$ and $\delta 2$) remained associated with the early improvement of post-infarction myocardial function after multivariate linear regression analysis. The present research indicated that omentin-1 represents a promising adipocytokine to retard negative cardiac remodeling after STEMI.

Key words: Omentin-1, STEMI, LVEF, CK−MB

Abbreviations: STEMI: ST-segment elevation myocardial infarction; I/R: ischemia/reperfusion; CAD: coronary artery disease; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; LAD: left anterior descending coronary artery; BMI: body mass index; TIMI: thrombolysis in Myocardial infarction; TNF-α: tumour necrosis factor-α; IL-6: interleukin-6; ELISA: enzyme-linked immunosorbent assay; CK-MB: muscle brain fraction of creatine kinase; NT-proBNP: N-terminal pro B-type natriuretic peptide; LVEF: left ventricular ejection fraction; AMI: acute myocardial infarction.

Address for correspondence: Yingxin Zhao, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University; Beijing Institute of Heart Lung and Blood Vessel Disease. #2, Anzhenlu, ChaoyangDistrict, Beijing 100029, China E-mail: zyingxinmi@163.com

Received: September 24, 2018 Accepted for publication: January 8, 2019

Introduction

Early reperfusion strategies and adjuvant pharmacological therapies limit myocardial injury and improve survival after ST-segment elevation myocardial infarction (STEMI)[1, 2]. However, reperfusion itself can induce additional damage to ischemic myocardium termed myocardial ischemia/reperfusion (I/R) injury, which also contributes to negative post-infarction myocardial remodeling and subsequent heart dysfunction[3, 4]. Recently, clinical and experimental studies have indicated that the novel adipocytokine omentin-1 plays an important role in regulating I/R injury[5].

Omentin-1, also named intelectin-1, is a novel adipocytokine with 313 amino acids, which is predominantly secreted by the human visceral adipose tissue rather than subcutaneous adipose tissue[6, 7]. Serum omentin-1 declines significantly in patients with obesity and obesity-associated disorders, including impaired glucose regulation, type 2 diabetes mellitus, and metabolic syndrome[7-9]. Serum levels of omentin-1 are also downregulated in patients with coronary artery disease (CAD)[10, 11], and upregulated in patients with the acute coronary syndrome (ACS)[12, 13]. Additionally, serum omentin-1 not only suppresses the process of atherosclerotic lesions[13, 14] but also may represent a novel biomarker inversely correlated with plaque instability[15]. Furthermore, serum omentin-1 also ameliorates myocardial damage and myocardial function after successful reperfusion in patients with STEMI[5].

However, there is no previous research concerning the kinetic changes in omentin-1 during the acute-phase of STEMI and the influence of it on myocardial damage and function after reperfusion. Therefore, the main purpose of this study was to address the correlations among the admission omentin-1, time-dependent kinetic changes in omentin-1, and myocardial function in patients with STEMI after successful primary percutaneous coronary intervention (PCI).

Methods

Subjects and Study Design

Between June 2017 and May 2018, patients with anterior STEMI were recruited from two hospitals in Beijing, China. Inclusion criteria were age >18 years, typical symptoms >30 minutes and <12 hours, electrocardiogram sign (ST-segment elevation >2 mm in at least two contiguous precordial leads or >1 mm in at least two contiguous limb leads), the infarct-related artery being the left anterior descending (LAD) artery and $<70\%$ stenosis of the non-infarct-related artery treated successfully by primary PCI. The success of primary PCI was defined as the recanalization of the LAD with $<30\%$ residual stenosis of the infarct-related lesion. Patients with a previous history of myocardial infarction and PCI were excluded. In addition, we also excluded the patients with a serious concomitant disease, including acute infection, malignancy, liver and renal impairment, chronic inflammatory disease and overt heart failure (Killip class Ⅲ or Ⅳ). Finally, a total of 52 patients were recruited into our study. Additionally, the patients were divided into two subgroups according to the median value of admission omentin-1 level. The study was approved by the regional Ethics Committee and conducted in compliance with the Declaration of Helsinki. In addition, we obtained the written informed consent from all the patients before enrollment.

Treatment and Clinical Evaluation

Doses of clopidogrel 600 mg, aspirin 300 mg and intravenous heparin (70−100 U/kg) were administered before primary PCI. Primary PCI was conducted by experienced interventionists in accordance with current practice guidelines and was carried out mainly through the radial artery. In addition, the patients with a high thrombus burden were recommended treatment with thrombus aspiration. The choice of stent type (new generation drug-eluting stents) and adjunctive pharmacologic treatment were placed at the discretion of the operator.

Demographic data, such as age, height, body weight, body mass index (BMI), blood pressure, and Killip class were all obtained upon admission. Medical history of smoking, diabetes, and hypertension were also recorded. In addition to total ischemic time, we also recorded single/multivessel disease, angiographic thrombolysis in myocardial infarction (TIMI) flow grade pre-operation and post-operation, the number of stents, as well as medications used at discharge.

BMI was obtained via weight in kilograms divided by the square of height in meters. From symptom onset to recanalization of infarction-associated artery was defined as total ischemic time. Multivessel disease was defined as $>50\%$ stenosis in at least one non-infarct-related artery. Killip class on admission and angiographic data were all at the discretion of two experienced cardiologists.

Blood Sampling and Biochemical Analysis

The venous blood samples were collected with serum separation hoses (Becton−Dickinson) on admission, at 24 hours, and at 72 hours after admission, followed by centrifuging for 15 minutes at 2500 g and storage of serum samples at −80℃. The aim of collecting these blood samples was to assay omentin-1 and two key inflammatory markers: tumor necrosis factor-α

Table 1. Baseline characteristics

	Total	Low omentin-1 group	High omentin-1 group	*p*-value
Number	52	26	26	
Age	55.12 ± 12.43	56.50 ± 13.89	53.73 ± 10.88	0.427
Male gender (%)	40 (76.9)	17 (65.4)	23 (88.5)	0.097
Systolic BP (mmHg)	120.46 ± 16.53	117.00 ± 15.63	123.92 ± 16.97	0.132
Diastolic BP (mmHg)	77.54 ± 12.39	75.50 ± 11.25	79.58 ± 13.33	0.239
Body mass index (kg/m^2)	26.43 ± 3.49	27.24 ± 3.55	25.62 ± 3.30	0.094
Hypertension (%)	27 (51.9)	14 (53.8)	13 (50.0)	1.000
Diabetes (%)	10 (19.2)	7 (26.9)	3 (11.5)	0.291
Current Smoking (%)	38 (73.1)	19 (73.1)	19 (73.1)	1.000
Pre-infarction angina (%)	15 (28.8)	9 (34.6)	6 (23.1)	0.541
Total ischemia time (min)	359.88 ± 206.47	374.46 ± 198.90	345.31 ± 216.71	0.616
Killip class Ⅱ on admission (%)	26 (50.0)	14 (53.8)	12 (46.2)	0.782
LVEF at 2 days post-STEMI (%)	55.29 ± 7.26	56.42 ± 6.71	54.15 ± 7.73	0.264
Laboratory examination				
White blood cells (10^9/L)	11.28 ± 3.35	11.86 ± 3.83	10.70 ± 2.74	0.212
Hemoglobin (g/L)	142.48 ± 18.33	139.69 ± 19.23	145.27 ± 17.29	0.277
Platelet (10^9/L)	238.31 ± 55.55	236.96 ± 59.53	239.65 ± 52.41	0.863
Fasting blood glucose (mmol/L)	6.81 ± 1.98	7.20 ± 2.14	6.41 ± 1.76	0.150
Triglycerides (mmol/L)	1.68 ± 1.05	1.94 ± 1.25	1.42 ± 0.76	0.079
LDL-C (mmol/L)	2.72 ± 0.92	2.68 ± 0.84	2.76 ± 0.76	0.724
HDL-C (mmol/L)	0.99 ± 0.16	0.96 ± 0.15	1.02 ± 0.17	0.199
Uric acid (mg/dl)	328.90 ± 85.43	333.00 ± 94.85	324.81 ± 76.52	0.733
Serum creatinine (umol/L)	59.04 ± 14.56	58.38 ± 15.68	59.69 ± 13.62	0.750
Peak CK-MB (U/L)	217.82 ± 141.81	257.58 ± 147.75	178.05 ± 126.12	0.042
NT-proBNP (pg/ml)	494.50 (249.25, 1610.00)	1040.00 (409.75, 1940.75)	426.00 (206.50, 918.25)	0.008
Angiographic data (%)				
Infarct-related artery (LAD)	52 (100.0)	26 (100.0)	26 (100.0)	1.000
Multivessel disease	17 (32.7)	9 (34.6)	8 (20.8)	1.000
Gensini Score	58.38 ± 20.97	61.62 ± 18.55	55.15 ± 23.04	0.271
Thrombus aspiration	3 (5.8)	1 (3.8)	2 (7.6)	1.000
Tirofiban	29 (55.8)	16 (61.5)	13 (50.0)	0.577
Stent implantation	52 (100.0)	26 (100.0)	26 (100.0)	1.000
The number of stent = 1	46 (88.5)	22 (84.6)	24 (92.3)	0.668
TIMI = 0, before PCI	42 (80.8)	23 (88.5)	19 (73.1)	0.291
TIMI < 3, after PCI	14 (26.9)	10 (38.5)	4 (15.4)	0.116
Medication, before AMI (%)				
Aspirin	4 (7.7)	3 (11.5)	1 (3.8)	0.610
Statin	8 (15.4)	3 (11.5)	5 (19.2)	0.703
ACEI/ARB	8 (15.4)	5 (19.2)	3 (11.5)	0.703
Beta-block	2 (3.8)	2 (7.7)	0 (0.0)	0.490
Metformin	6 (11.5)	5 (19.2)	1 (3.8)	0.191
Other hypoglycemic agents	2 (3.8)	2 (7.7)	0 (0.0)	0.490
Insulin	1 (1.9)	0 (0.0)	1 (3.8)	1.000
Medication, discharge (%)				
Aspirin	52 (100.0)	26 (100.0)	26 (100.0)	1.000
Clopidogrel	52 (100.0)	26 (100.0)	26 (100.0)	1.000

(Cont. Table 1)

	Total	Low omentin-1 group	High omentin-1 group	*p*-value
Medication, discharge (%)				
Statin	52 (100.0)	26 (100.0)	26 (100.0)	1.000
ACEI/ARB	43 (82.7)	22 (84.6)	21 (80.8)	1.000
Beta-block	50 (96.2)	25 (96.2)	25 (96.2)	1.000
Metformin	7 (13.5)	6 (23.1)	1 (3.8)	0.099
Other hypoglycemic agents	2 (3.8)	2 (7.7)	0 (0.0)	0.490
Insulin	1 (1.9)	0 (0.0)	1 (3.8)	1.000

Data are presented as Mean ± SD, median (low quartile ,upper quartile), or number (%)
BP blood pressure, LVEF left ventricular ejection fraction, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, CK-MB muscle brain fraction of creatine kinase, NT-proBNP N-terminal pro B-type natriuretic peptide, LAD left anterior descending coronary artery, TIMI thrombolysis in myocardial infarction, PCI percutaneous coronary intervention, AMI acute myocardial infarction, ACEI/ARB angiotensin-converting enzyme inhibitor/angiotensin receptor blocker

(TNF-α) and interleukin-6 (IL-6). The concentrations of serum omentin-1 and inflammatory cytokines were measured in duplicate by commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (BLUE GENE, Shanghai, China). Both ELISA intra-assay and inter-assay coefficients of variation in our study were < 5%. Finally, we defined (admission omentin-1 level) - (serum omentin-1 at 24 hours after admission) as $\delta 1$ and (admission omentin-1 level) - (serum omentin-1 at 72 hours after admission) as $\delta 2$.

Peak MB fraction of creatine kinase (CK−MB) correlated well with infarct size and prognosis after acute myocardial infarction[16]. Thus, CK−MB levels were measured on admission, the following evening, and morning to identify peak CK−MB. N-terminal pro-B-type natriuretic peptide (NT-proBNP) measured 2 to 4 days following STEMI independently forecast myocardial function and 2-year survival, which is superior to BNP and other cardiac peptides[17, 18]. So, NT-proBNP at day 3 post-STEMI was determined. The rest of the routine biochemical parameters were also determined in the Central Laboratory of Beijing Anzhen Hospital.

Evaluation of Myocardial Function with Echocardiography

Doppler echocardiography was performed by the same two experienced doctors at 2 days and 3 months post-STEMI. Standard echocardiography views were obtained with the supervision of experienced cardiologists. Left ventricular ejection fraction (LVEF) was acquired with the modified Simpson biplane method. The change in LVEF was regarded as (LVEF at 3 months post-STEMI) − (LVEF at 2 days post-STEMI).

Statistical Analysis

Normality distribution of continuous variables was assessed by Kolmogorov−Smirnov test. Continuous data are expressed as the mean ± standard deviation or median value with interquartile range. Mean values of the data were compared by independent-sample *t*-tests but median values of variables were compared by the Mann−Whitney *U* test. Categorical variables are presented as percentages and were analyzed by chi-squared tests. One-way analysis of variance was used to test the trend of time course of serum omentin-1. The association between variables was assessed by Pearson correlation coefficients. In addition, the associations between variables and LVEF change from baseline to 3 months were determined by univariate analysis and multivariate linear regression analysis. All the statistical analyzes were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). *P* values < 0.05 were considered statistically significant.

Results

Baseline Characteristics

The baseline characteristics of patients recruited into this study are presented in **Table 1**. The mean age of the recruited patients was 55.12 ± 12.43 years old, and 76.9% were male. The prevalence of current smoker, hypertension, and diabetes were 73.1%, 51.9%, and 19.2%, respectively. In addition, peak CK−MB was 217.82 ± 141.8 U/L and the median NT-proBNP at day 3 post-STEMI was 494.50 (249.25, 1610.00) pg/ml. Furthermore, 67.3% of the recruited patients had single vessel disease. Most importantly, the mean total ischemic time was 359.88 ± 206.47 minutes, which revealed that all the patients recruited obtained timely reperfusion. We also divided the patients into two subgroups. Except for peak CK−MB, NT-proBNP, and

change in LVEF from baseline to 3 months, no significant differences were observed between the two subgroups.

Change in Serum Omentin-1 in Acute STEMI

The sequential change in serum omentin-1 concentration in the recruited patients was tested first. The mean concentration of serum omentin-1 on admission, at 24 hours, and at 72 hours after admission was 934.75 ± 249.82 pg/ml, 833.87 ± 197.27 pg/ml and 844.80 ± 220.80 pg/ml, respectively (p_{trend} = 0.044). As indicated in **Fig. 1A**, admission omentin-1 was the highest, while omentin-1 declined rapidly the following 72 hours. Additionally, as shown in **Fig. 1B** and **Fig. 1C**, baseline serum omentin-1 positively correlated with $\delta 1$ (r = 0.626, p < 0.001) and $\delta 2$ (r = 0.473, p < 0.001).

Serum Omentin-1 and Inflammatory Cytokine Analysis

Correlation between serum omentin-1, time-dependent change in omentin-1, and inflammatory markers are presented in **Table 2**. For admission omentin-1 with inflammatory cytokines, admission omentin-1 not only correlated positively with admission IL-6 (r = 0.786, p < 0.001) and admission TNF-α (p = 0.565, p < 0.001) but also correlated positively with IL-6 and TNF-α at other time points. In addition, omentin-1 concentration at 24 and 72 hours after admission also had consistent correlation with inflammatory cytokines at each time point. Furthermore, there were consistent correlations between $\delta 1$ and IL-6 on admission (r = 0.519, p < 0.001), at 24 hours (r = 0.421, p = 0.002), and at 72 hours (r = 0.489, p < 0.001) after admission. $\delta 1$ also correlated with admission TNF-α (r = 0.362, p = 0.008) and TNF-α at 72 hours (r = 0.275, p = 0.048) after admission. For $\delta 2$, there were also positive correlations with IL-6 on admission (r = 0.294, p = 0.034) and at 24 hours (r = 0.297, p = 0.033) after admission.

Association between Omentin-1 and Peak CK−MB with NT-proBNP

As shown in **Table 1**, compared with the low admission omentin-1 group, the high admission omentin-1 subgroup had a lower level peak CK−MB (178.05 ± 126.12 U/L vs. 257.58 ± 147.75 U/L, p = 0.042). As shown in **Fig. 2A** and **Fig. 2B**, there were inverse correlations between $\delta 1$ (r = −0.280, p = 0.044), $\delta 2$ (r = −0.294, p = 0.034) and peak CK−MB. Additionally, as presented in **Table 1**, the patients in the subgroup with high admission omentin-1 also exhibited a lower NT-proBNP level [426.00 (206.50, 918.25) pg/ml vs. 1040.00 (409.75, 1940.75) pg/ml, p = 0.008] measured at 3 days post-STEMI. As revealed in **Fig. 2C** and **Fig. 2D**, there were also negative correlations between $\delta 1$ (r = −0.384,

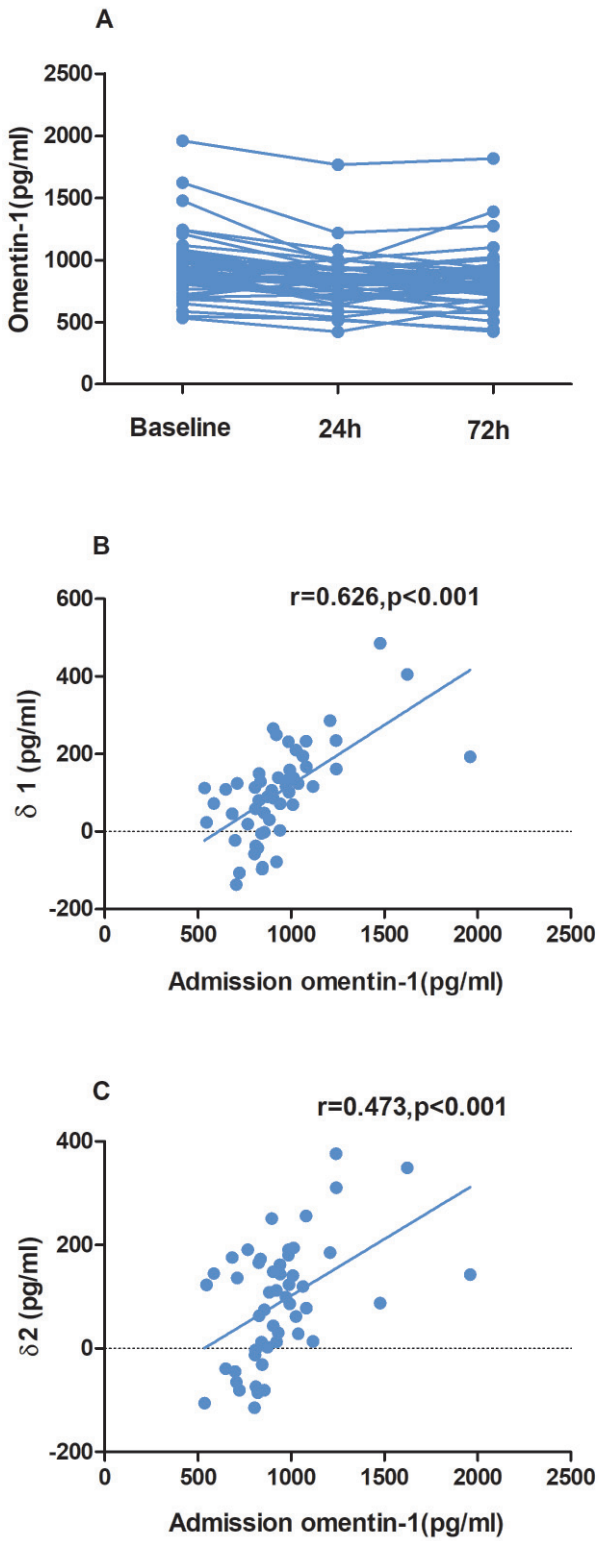

Fig. 1. The sequential change in serum omentin-1 concentration (A). The association between admission omentin-1 and $\delta 1$ (B) as well as $\delta 2$ (C). (Admission omentin-1 level) - (serum omentin-1 at 24 hours after admission) as $\delta 1$ and (admission omentin-1 level) - (serum omentin-1 at 72 hours after admission) as $\delta 2$.

Table 2. Correlation between serum omentin-1 , time-dependent change of omentin-1 and inflammatory markers

	Baseline omentin-1	Omentin-1 (24 h)	Omentin-1 (72 h)	δ1	δ2
Admission IL-6	0.786 (<0.001)	0.664 (<0.001)	0.741 (<0.001)	0.519 (<0.001)	0.294 (0.034)
IL-6 (24 h)	0.778 (<0.001)	0.715 (<0.001)	0.732 (<0.001)	0.421 (0.002)	0.297 (0.033)
IL-6 (72 h)	0.797 (<0.001)	0.698 (<0.001)	0.772 (<0.001)	0.489 (<0.001)	0.265 (0.058)
Admission TNF-α	0.565 (<0.001)	0.483 (<0.001)	0.509 (<0.001)	0.362 (0.008)	0.257 (0.066)
TNF-α (24 h)	0.541 (<0.001)	0.535 (<0.001)	0.474 (<0.001)	0.229 (0.103)	0.270 (0.053)
TNF-α (72 h)	0.555 (<0.001)	0.524 (<0.001)	0.526 (<0.001)	0.275 (0.048)	0.197 (0.163)

IL-6 interleukin-6, TNF-α tumor necrosis factor-alpha, δ1 as (admission omentin-1 level) - (omentin-1 level at 24 hour after admission), δ2 as (admission omentin-1 level) - (omentin-1 level at 72 hour after admission).

$p=0.005$), δ2 ($r=-0.420$, $p=0.002$) and NT-proBNP measured at 3 days post-STEMI.

Correlation between Omentin-1 and the Early Change in Myocardial Function

After calculating the change in LVEF from baseline to 3 months post-STEMI, as shown in **Fig. 3A**, our data demonstrated that the absolute change in LVEF improved significantly in the high admission omentin-1 group compared to the low admission omentin-1 group (5.27%±7.11% vs. −0.46%±7.84%, $P=0.008$). Additionally, as indicated in **Fig. 3B**, the global LVEF in the high admission omentin-1 group improved significantly (59.41%±7.23% vs. 54.15%±7.73%, $p=0.014$), but the low admission omentin-1 group was without such improvement (55.96%±8.84% vs. 56.42%±6.71%, $p=0.833$).

As for the time-dependent change in serum omentin-1 with LVEF at 3 months post-STEMI, there were moderate correlations between δ1 ($r=0.392$, $p=0.004$), δ2 ($r=0.382$, $p=0.005$), and LVEF at 3 months post-STEMI (**Fig. 4A**, **Fig. 4B**). Most importantly, moderate but high associations were also observed between δ1 ($r=0.346$, $p=0.012$), δ2 ($r=0.439$, $p=0.001$), and change in LVEF from baseline to 3 months post-STEMI (**Fig. 4C**, **Fig. 4D**). Last but not the least, in multivariate linear regression model, which included age, sex, and other variables with $p<0.05$ in univariate analysis as shown in **Table 3**, δ1 (Beta=0.026, 95% CI 0.011 to 0.041, $p=0.001$) remained associated with the absolute change in LVEF from baseline to 3 months post-STEMI in multiple linear regression model A. Additionally, in model B, δ2 (Beta=0.024, 95% CI 0.009 to 0.038, $p=0.003$) also correlated with the change in LVEF from baseline to 3 months post-STEMI.

Discussion

This is the first study to manifest time-dependent kinetic changes in omentin-1 levels associated with the early improvement of myocardial function in patients with their first anterior STEMI after primary PCI. In the present study, we demonstrated several relationships. First, serum omentin-1 was the highest on admission but declined significantly in the following 72 hours. Additionally, admission omentin-1 level correlated positively with time-dependent kinetic changes in omentin-1 level (δ1 and δ2). Second, peak CK−MB and NT-proBNP at 72 hours post-STEMI were significantly lower in the high admission omentin-1 subgroup. Additionally, the high admission omentin-1 group improved markedly in the change in LVEF compared to the low omentin-1 group. Third, time-dependent kinetic changes in omentin-1 level (δ1 and δ2) had negative correlations with peak CK−MB and NT-proBNP at 72 hours post-STEMI. Furthermore, the δ1 and δ2 not only correlated positively with LVEF at 3 months post-STEMI but also correlated with the change in LVEF.

Accumulating evidence indicated omentin-1, as a novel adipocytokine with cardioprotective effects, is downregulated in people with atherosclerosis and risk factors associated with atherosclerosis, including obesity, diabetes, hypertension, and dyslipidemia[7, 19, 20]. Watanabe *et al.* and Du *et al.* further revealed that the concentration of omentin-1 was declined in the serum, epicardial adipose tissue and coronary endothelium in patients with CAD[11, 13]. However, the omentin-1 concentration increased markedly in the medial layer vascular smooth muscle and macrophage-derived foam cells within advanced plaques and circulating blood in patients with ACS[13]. Saddic *et al.* and Kadoglou *et al.* further showed that serum omentin-1 increased significantly after acute myocardial ischemia[12, 21]. All these evidence suggests that serum omentin-1 not only was a passive risk factor for chronic CAD but was also an acute-phase reactant with cardioprotective effects during ACS. In addition, metformin may raise serum omentin-1 level in patients with acute myocardial infarction (AMI) and decrease the serum cardiac troponin concentration[22]. Weight loss, statin, and other hypoglyce-

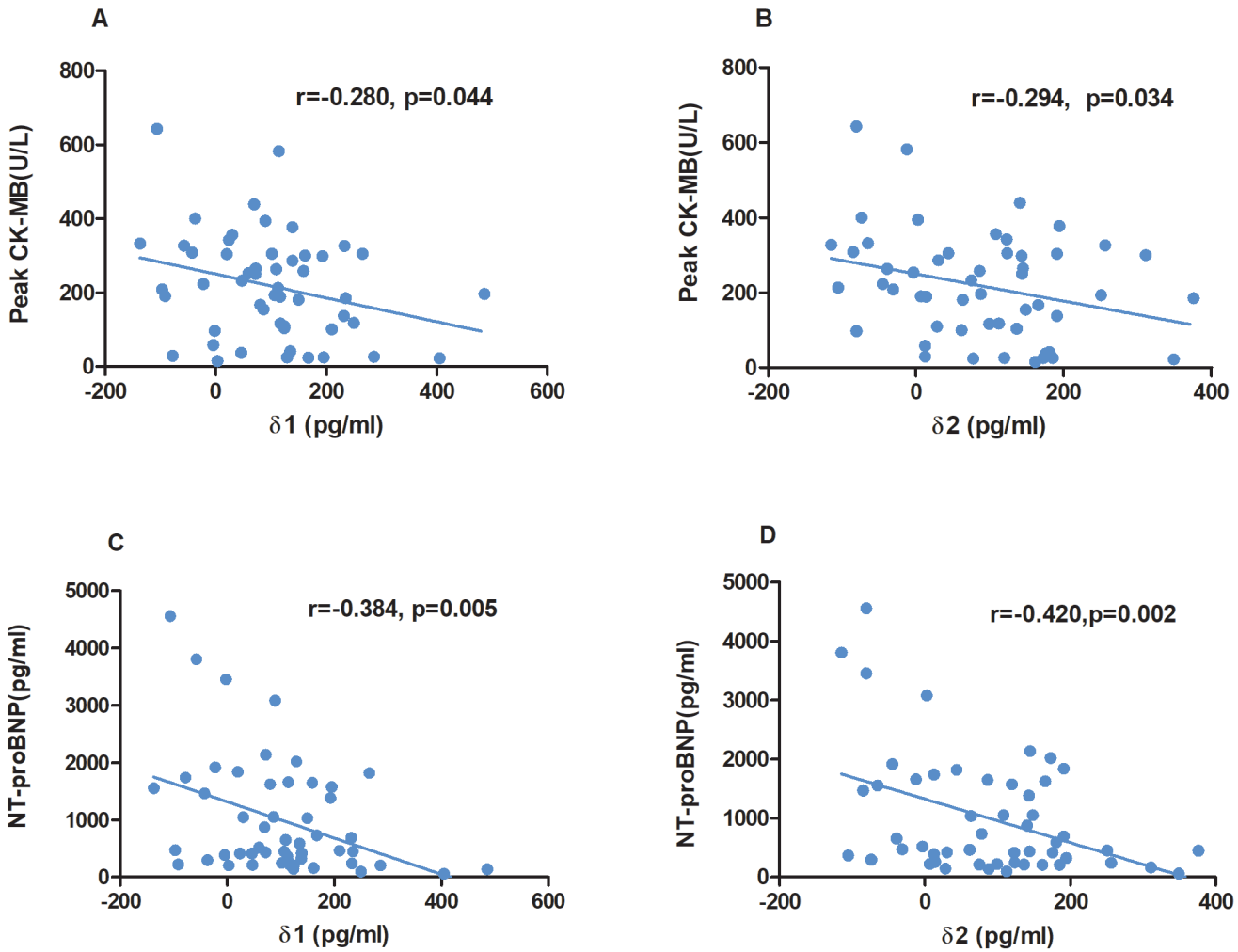

Fig. 2. orrelation between δ1 (A), δ2 (B) and peak CK−MB. Association between δ1 (C), δ2 (D) and NT-proBNP measured at 3 days post-STEMI. (Admission omentin-1 level) - (serum omentin-1 at 24 hours after admission) as δ1 and (admission omentin-1 level) - (serum omentin-1 at 72 hours after admission) as δ2; CK−MB, muscle brain fraction of creatine kinase; NT-proBNP, N-terminal pro B-type natriuretic peptide; STEMI, ST-segment elevation myocardial infarction

mic agents, such as liraglutide and exenatide, may also increase serum omentin-1 level[23-26], but the evidence in patients with AMI was limited.

As we all know, myocardial I/R injury is characterized by an acute level of high-grade inflammatory response with rapid formation and release of TNF-α and IL-6[27, 28]. In our present study, anti-inflammatory mediator omentin-1 correlated positively with the two key cytokines, TNF-α and IL-6, during the acute-phase of STEMI. Therefore, our study further confirmed that omentin-1 may act as an acute-phase reactant to counteract the inflammatory response for the sake of cardiovascular protection during the process of myocardial I/R.

Now, accumulating evidence has indicated that baseline omentin-1 increased significantly in circulating blood in patients with ACS[12, 13, 21]. Our present study extends prior findings by indicating that increased admission omentin-1 declined transiently during the acute-phase of STEMI. The accumulation of omentin-1 in injured cardiovascular tissues as suggested by *in vivo* and *in vitro* experiments may[13], at least in part, account for the post-procedural transient decrement of serum omentin-1. Additionally, in patients with STEMI, the baseline adiponectin also decreased transiently, maybe due to the accumulation of adiponectin in injured cardiovascular tissues mediated by T-cadherin[29-32]. Thus, this study calls for a future study to determine the mediators that play a critical role in cardiovascular tissue accumulation of omentin-1.

Kataoka *et al.* showed that high levels of circulating omentin-1 in mice limited myocardial injury and

myocardial infarction size[5]. In our present study, we have shown that in patients with STEMI, peak CK−MB also declined significantly in the subgroup with a high level of admission omentin-1. Natsukawa *et al.* reported that the transient decrement of adiponectin from baseline to bottom during acute-phase STEMI was significantly associated with the area under the curve of CK−MB[30]. In our present study, both $\delta 1$ and $\delta 2$ also correlated negatively with peak CK−MB. Subsequently, we found the absolute change in LVEF from baseline to 3 months post-STEMI improved significantly in patients with a high level of baseline omentin-1. Similar to our finding, Kataoka *et al.* also confirmed that high levels of serum omentin-1 in post-STEMI patients were correlated with the improvement of myocardial function[5]. Most importantly, our study demonstrated that time-dependent changes in omentin-1, $\delta 1$, and $\delta 2$ correlated positively with the improvement of myocardial function for the first time. In addition, as Narumi et.al reported, high baseline omentin-1 level may have beneficial effects on cardiac prognosis in patients with heart failure or reduced LVEF[33], whereas the effects of time-dependent change in omentin-1 in patients with heart failure were unknown.

Omentin-1 not only stimulated vasodilation of the isolated aorta via endothelium-dependent NO but also improved endothelial cell function and the process of revascularization in circumstances of acute ischemia via the AKt/eNOS pathway[34, 35]. For the anti-inflammatory effect, omentin-1 stimulated the differentiation of macrophages into the M2 phenotype exerting an overwhelming anti-inflammatory action, rather than the M1 phenotype with proinflammatory action[13]. In addition, omentin-1 attenuated the vascular inflammatory response via various kinds of intracellular signaling pathways[36-38]. Therefore, the anti-inflammatory and modulation of endothelial function features may account, at least in part, for omentin-1 being protective against I/R injury. In addition to myocardial infarction, other forms of cardiomyocyte death, including apoptosis, autophagy, and necroptosis were also responsible for the final infarct size and myocardial dysfunction in the post-STEMI patients[3]. Omentin-1 can suppress the apoptosis of the myocyte associated with I/R via the mutually independent AMPK and Akt signal pathways, which was also responsible for the improvement in myocardial damage and function post-STEMI[5]. Whether omentin-1 has an influence on autophagy and necroptosis calls for further study. Furthermore, the cross talk between omentin-1 and other adipocytokines may also participate in regulating myocardial necrosis and subsequent myocardial remodeling, which needs further confirmation by large-scale clinical studies and *in vitro* experiments[12, 39].

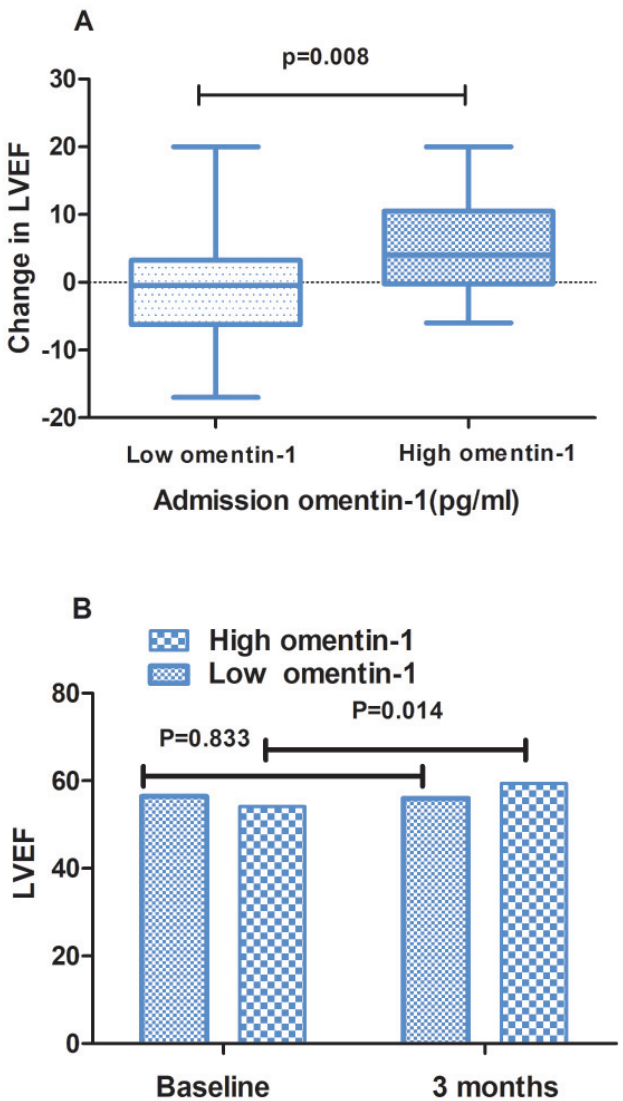

Fig. 3. The change in LVEF from baseline to 3 months in low and high admission omentin-1 group (A). The LVEF in patients with low and high omentin-1 group at baseline and 3 months post-STEMI (B). LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction.

Watanabe *et al.* showed through *in vivo* and *in vitro* experiments that almost all exogesly infused omentin-1 accumulated in the injured cardiovascular tissue, including the adventitia tissue of the aorta, myocardium and macrophages, without significant change in serum omentin-1 levels[13]. In STEMI patients, examination of the accumulation of omentin-1 in the infarct region was impossible, but a transient decrement of serum omentin-1 in STEMI patients may imply the accumulation of omentin-1 in the infarct region. The

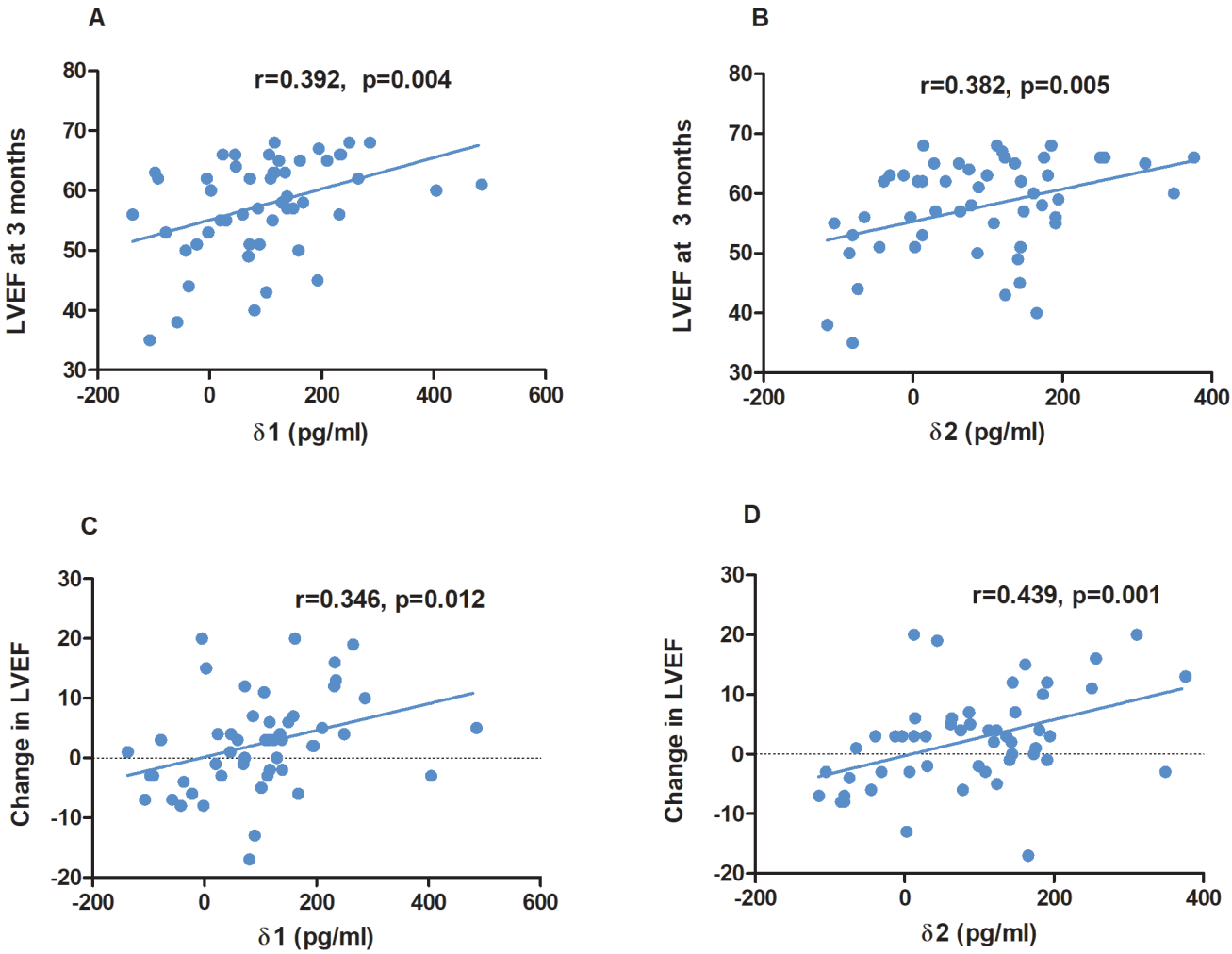

Fig. 4. Correlation between $\delta 1$ (A), $\delta 2$ (B) and LVEF at 3 months after procedure. Correlation between $\delta 1$ (C), $\delta 2$ (D) and the change in LVEF. (Admission omentin-1 level) - (serum omentin-1 at 24 hours after admission) as $\delta 1$ and (admission omentin-1 level) - (serum omentin-1 at 72 hours after admission) as $\delta 2$; LVEF, left ventricular ejection fraction.

accumulation of omentin-1 in the infarct region may exert cardioprotective effects. As shown in **Fig. 2** and **Fig. 4**, a transient decrement of serum omentin-1 ($\delta 1$ and $\delta 2$) not only had inverse correlation with peak CK−MB and NT-proBNP at 72 hours post-STEMI, but also correlated positively with LVEF at 3 months post-STEMI and the early improvement in LVEF, suggesting the possibility that accumulation of omentin-1 may reduce myocardial necrosis and improve post-infarction myocardial function.

In our present study, admission omentin-1 and inflammatory cytokines (TNF-α and IL-6) all have positive effects on the cardiovascular tissue accumulation of omentin-1. If we can identify the mediators that play a critical role in cardiovascular tissue accumulation of omentin-1 during I/R injury, we may open up a novel therapeutic window for I/R injury.

Study Limitations

There are several limitations to this study. First, this was a cross-sectional study with a relatively small sample size. To further elucidate the relationship between time-dependent kinetic changes in omentin-1 level and the recovery of myocardial function large scale clinical studies are required. Second, we only enrolled patients with first anterior STEMI who underwent primary PCI, which may affect the outcome because we may have missed some critical STEMI patients. Third, the LVEF was only assessed by Doppler echocardiography, future studies should apply cardiac magnetic resonance imaging or single-photon emission computed

Table 3. Correlation between absolute change of LVEF and variables using univariate and multivariate linear regression analysis

Variable	Absolute change of LVEF from baseline to 3 months post-STEMI					
Model A	Univariate			Multivariate ($R^2=0.532$, $p<0.001$)		
	Beta	95%CI	*P*-value	Beta	95%CI	*P*-value
Age	−0.011	−0.193 to 0.171	0.902	−0.094	−0.245 to 0.058	0.219
Sex	−6.808	−11.756 to −1.861	0.008	−2.947	−7.396 to 1.051	0.189
FBG	−1.405	−2.473 to −0.337	0.011	−0.595	−1.516 to 0.326	0.200
HDL	−14.919	−28.418 to −1.420	0.031	−15.448	−26.684 to −4.211	0.008
Baseline LVEF	−0.465	−0.747 to −0.183	0.002	−0.488	−0.732 to −0.243	<0.001
$\delta 1$	0.022	0.005 to 0.040	0.012	0.026	0.011 to 0.041	0.001
Admission omentin-1	0.006	−0.003 to 0.015	0.206			
Admission IL-6	0.033	−0.024 to 0.089	0.256			
Admission TNF-α	0.007	−0.029 to 0.043	0.682			
Mode B	Univariate			Multivariate ($R^2=0.519$, $p<0.001$)		
	Beta	95%CI	*p*-value	Beta	95%CI	*p*-value
Age	−0.011	−0.193 to 0.171	0.902	−0.037	−0.187 to 0.114	0.625
Sex	−6.808	−11.756 to 1.861	0.008	−4.509	−8.934 to −0.085	0.046
FBG	−1.405	−2.473 to −0.337	0.011	−0.722	−1.460 to 0.195	0.120
HDL	−14.919	−28.418 to −1.420	0.031	−7.606	−18.283 to 3.070	0.158
Baseline LVEF	−0.465	−0.747 to −0.183	0.002	−0.444	−0.692 to −0.196	0.001
$\delta 2$	0.030	0.013 to 0.048	0.001	0.024	0.009 to 0.038	0.003
Admission omentin-1	0.006	−0.003 to 0.015	0.206			
Admission IL-6	0.033	−0.024 to 0.089	0.256			
Admission TNF-α	0.007	−0.029 to 0.043	0.682			

LVEF left ventricular ejection fraction, CI confidence interval , FBG fasting blood-glucose, HDL high-density lipoprotein, $\delta 1$ as (omentin-1 leve1 on admission)−(omentin-1 level at 24 hours after admission), IL-6 interleukin-6, TNF-α tumor necrosis factor-alpha, $\delta 2$ as (admission omentin-1 level)-(omentin-1 level at 72 hours after admission).

tomography imaging to assess LVEF exactly and quantify the infarct size. Fourth, our research failed to determine whose omentin-1 levels might be lower before the onset of AMI, which needs further investigation by future research. Finally, after multiple linear regression analysis, $\delta 1$ and $\delta 2$ remained associated with the absolute change in LVEF from baseline to 3 months post-STEMI. However, the influence of residual confounding variables cannot be excluded.

Conclusions

In patients with their first anterior STEMI who underwent primary PCI, the early recovery of post-infarction myocardial function were significantly associated with admission omentin-1 levels and the time-dependent change in serum omentin-1. Through multivariate linear regression analysis, only the time-dependent change in omentin-1 ($\delta 1$ and $\delta 2$) remained associated with the early improvement of post-infarction myocardial function. Our data suggested that omentin-1 is a novel adipocytokine that suppresses myocardial I/R injury and subsequent negative remodeling. Future studies are warranted to further elucidate the underlying mechanism between omentin-1 and myocardial I/R injury as well as subsequent negative remodeling. In addition, identifying the key mediators regulating cardiovascular tissue accumulation of omentin-1 is also very important.

Acknowledgement

We convey thanks to the following doctors, Meng Li, Kun Wang, Xue-Jie Wang, and Jie Sun for their help in collecting the blood sample. This work was supported by the Beijing Municipal science and Technology Commission (NO. Z171100000417042).

Conflict of Interest

The authors declare that they have no competing interests.

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