Association of serum leptin and resistin levels among obese Saudi patients with acute myocardial infarction in Asir region

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ABSTRACT

In the current scenario, the importance of cardiac biomarkers in diagnosing, assessing, and managing people with cardiovascular discomfort is required. This cross-sectional study examined the relationship between serum leptin and resistin levels among obese people with acute myocardial infarction (AMI) with varying body mass index (BMI). The cardio and diabetic biomarkers among the 77 Saudi patients with hypoxia who lived in the Asir region were analyzed in the study. The patients were categorized into three groups, namely, group 1 (control), group 2 (AMI with normal BMI), and group 3 (AMI with varying BMI). Our results showed a positive correlation between serum glucose, HbA1C, triglycerides, Troponin-I (cTnI), creatine kinase MB (CK-MB), leptin, and resistin in patients with AMI. We also observed significantly lower HbA1C, cholesterol, and insulin values in groups 2 and 3. A statistical difference between the groups with and without AMI and between the genders was noticed. BMI with leptin showed a positive connection in group 3 but no association was observed for groups 1 and 2. A stronger relationship between BMI and leptin levels in men in Group 3 than in women was observed. In all three groups, resistin levels did not correlate with BMI. Thus, circulating leptin concentrations do not significant impact AMI compared to participants with and without AMI. However, resistin levels were considerably higher in obese individuals with AMI. Therefore, we suggest that resistin can be used as a pro-inflammatory marker to detect AMI disorder with varying BMI and as a prognostic marker associated with AMI.

Introduction

Atherosclerosis, pulmonary hypertension, and heart failure are all preceded by hypoxia (a lack of oxygen at higher altitudes), which is a common risk factor for a variety of coronary artery disease (CAD) disorders (1). It is perceived that the leading cause of mortality in the world is mainly due to cardiovascular disease (CVD). Myocardial infarction and hypertrophy, both linked with high mortality, are the two most common causes of CVD (2). More people are becoming sedentary, which increases the risk of CVD and its linked disorders, such as diabetes and obesity (3). The World Health Organization (WHO) states that obesity has quadrupled since 1975. Almost 39% of individuals globally (1.9 billion) were overweight in 2016 (4). Studies have shown that obesity, especially abdominal adiposity, may have a role in metabolic disorders and CAD (5).

Diabetes is connected with an increased risk of CVD, although insulin resistance and inflammation are two of the most significant pathogenic variables (6). Obesity and diabetes are associated with releasing adipokines, a group of cytokines generated by adipose tissue (7). In recent years, adipokines, which comprise leptin, resistin, adiponectin, and tumor necrosis factor-α, have been identified as the biggest and most active signaling molecules released from the body's endocrine organs (8). Over the past two decades, Leptin has been implicated in several studies as a key player in the relationship between obesity, inflammation, metabolic syndrome, and CVD (4). Both obesity and type-2 diabetes mellitus (T2DM) are substantial modifiable risk factors for acute myocardial infarction

(AMI), which is characterized by escalating levels of biochemical markers (9). Studies on adipokines and obesity have demonstrated that higher resistin and leptin levels in abdominal fat depots are associated with an increased body mass index (BMI) (5,10).

High levels of leptin in the blood (hyperleptinemia) and low levels of the hormone adiponectin are often seen in patients with obesity (11,12). Serum levels of leptin and resistin increase in cardiovascular events such as AMI and are therefore considered modifiable risk factors for AMI (13-15). In clinical studies, the connection between coronary heart disease (CHD) severity and serum resistin levels has received considerable attention. This molecule is a pro-inflammatory adipokine (16-18). In prospective investigations, high serum resistin levels have also been reported to predict cardiovascular events, but with some discrepancies (19,20). Leptin reduces food intake and increases energy expenditure by centrally acting on the hypothalamus, and its levels are closely correlated with the mass of white adipose tissue (21). The inflammatory and pro-atherogenic characteristics of leptin and resistin are believed to contribute significantly to CVD (3,22). Myocardial ischemia/reperfusion (I/R) damage has been cardioprotective by these adipose tissue-derived molecules. They may play a role in cardiac remodeling by inhibiting myocardial hypertrophy in CVD (23).

Non-diabetic people may have different risk factors for CAD than people with T2DM. Therefore, whether leptin and resistin play a role in the development of AMI must be answered for patients associated with hypoxia. In order to answer this issue, we reviewed data from recently diagnosed AMI and obese Saudi patients. In the current study, a cross-sectional study among AMI and obesity patients living in Asir region was studied to see how leptin and resistin levels vary with varying BMIs. This study looks at the relationship between leptin and resistin levels and the risk of having an AMI in Saudi obese people living in high altitudes.

Materials and Methods

Study design and participants

We conducted a cross-sectional, population-based study of individuals with AMI and obesity who live at higher altitudes in Abha, Asir Province, Kingdom of Saudi Arabia, between 2020 and 2021. Regional Committee approved the study for Research Ethics in Directorate Health Affairs-Asir Region (with the approval number REC-NO:13-2-2021). The Research Ethical Committee at King Khalid University also has approved this study (with the approval number ECM#2019-13). This study involved 77 participants from the Prince Faisal Bin Khalid Cardiac Center (PFBKCC) in Abha, Saudi Arabia. All these samples were obtained after finishing all necessary tests in PFBKCC. The patient's demographic data were collected from the medical records, including gender, age, weight, and height, for calculating body mass index (BMI) without affecting the patient privacy details. BMI was calculated as weight (kg) divided by height squared (m²) according to WHO. BMI was normal if it was below 25 kg/m² and overweight if the result fits between 25 - 29.9 kg/m², while it is obese if the BMI reaches 30 kg/m2 or more.

Inclusion and exclusion criteria

Patients below the age of 19 years were not included in the study. Also, patients with a BMI of more than 25 kg/m² were considered for the study. Patients with cancer, immunological disorders, and severe health issues were not considered for the study.

Sample collection and storage

The participant samples were divided into three groups based on the aim of this study, as illustrated in Figure 1. Group 1 includes a control based on the normal BMI of healthy volunteers, N=15 (8 male and 7 female). Group 2 comprises patients with AMI and normal BMI, N=10 (8 male and 2 female). Group 3 has patients diagnosed with AMI with obesity, N= 52 (40 male and 12 female). The serum samples from all the participants were stored in non-anticoagulated tubes, separated by centrifugation, and stored in a -80ºC freezer until further analysis.

Measurements and assessment of biochemical markers

Biochemical parameters, including glucose and cholesterol, were measured using an automated biochemical analyzer (Beckman coulter, AU480). Glycosylated hemoglobin (HbA1c), CK-MB, lactate dehydrogenase (LDH), insulin, and triglycerides (TG) were assessed using a biochemistry Autoanalyzer (Abbott, Architect PLUS, c4000). While the Troponin I (cTnI) was measured by Abbott Point of Care,i-STAT 1 analyzer (USA) at PFBKCC.

Estimation of leptin and resistin serum levels

Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to determine the concentration of Leptin and Resistin following the manufacturer's instructions (Novex by Life Technologies, Human Leptin ELISA kit, Cat.#KAC2281 (96 tests); Human Resistin ELISA kit, Cat.#KHP0051 (96 tests)). These were carried out using FLUOstar® Omega Plate Reader by BMG LABTECH in the Central Research Laboratory at the College of Applied Medical Sciences at King Khalid University, Saudi Arabia. The procedure and the calculations of the serum leptin and resistin levels were performed as previously (24). Briefly, serum samples were diluted to 1:100 with standard diluent buffer. Microtitre plates were used to estimate the concentration of leptin and resistin, where 100 μl of standards, samples, and controls were added. The following procedure was followed individually to estimate the concentration of leptin and resistin. 100 μl of biotinylated anti-Hu leptin or human resistin detection antibody solution was added to each well and incubated
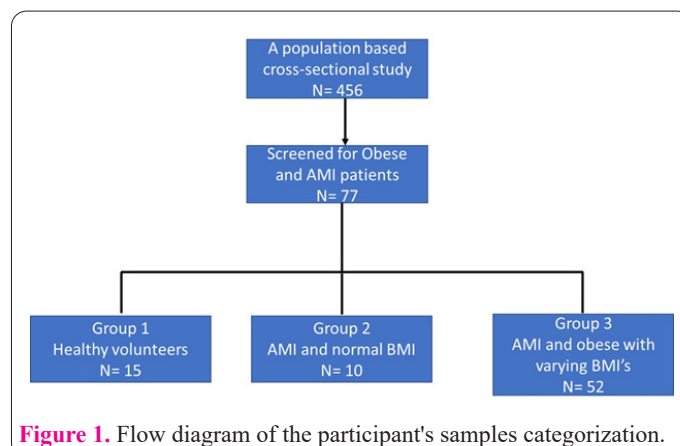

Figure 1. Flow diagram of the participant's samples categorization.

Table 1. Cross-sectional study: Baseline and demographic characteristics of study subjects.

Parameters (reference range)	Group 1			Group 2			Group 3		
	F (n=8)	M (n=7)	All (n=15)	F (n=2)	M (n=8)	All (n=10)	F (n=12)	M (n=40)	All (n=52)
Age	29.75 ±4.71	37.25 ± 2.28	33.50 ± 5.27	63.00 ±5.00	68.00 ±16.79	67.00 ± 15.31	63.17 ±9.40	62.23 ±13.27	62.44 ±12.49
Weight	59.00 ±7.28	69.25 ±5.72	64.13 ±8.31	55.50 ±1.50	61.96 ±8.34	60.67 ±7.93	76.17 ±11.31	82.18 ±12.20	80.79 ±12.27
BMI	22.70 ±2.60	24.23 ±0.63	23.47 ±2.04	21.10 ±1.38	22.77 ±2.06	22.44 ±2.06	30.13 ±5.01	29.41 ±3.30	29.58 ±3.78
Glucose (74-120 mg/dL)	89.48 ±4.48	106.39 ±17.81	97.93 ±15.49	192.38 ±80.41	221.41 ±158.42	215.60 ±146.64	223.91 ±109.17	204.53 ±89.04	209.00 ±94.42
HbA1C (4.3-6.2%)	5.30 ±0.00	5.55 ±0.25	5.43 ±0.22	10.15 ±4.15	7.98 ±3.00	8.41 ±3.38	8.16 ±2.08	11.55 ±24.33	10.77 ±21.41
TG (0.00-150 mg/dL)	67.00 ±17.29	118.25 ±35.59	92.63 ±37.94	129.00 ±6.00	125.44 ±83.55	126.15 ±74.79	149.68 ±60.65	137.06 ±62.80	139.97 ±62.53
CHOL (0.00- 200 mg/dL)	183.51 ±29.32	218.82 ±15.35	201.16 ±29.31	242.08 ±0.00	171.34 ±43.72	179.20 ±46.83	193.77 ±37.50	185.86 ±54.29	187.68 ±51.02
Tropo I (0.01- 0.023 ng/mL)	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	7.87 ±4.88	17.44 ±18.27	15.53 ±16.93	2.43 ±3.37	30.62 ±117.62	24.11 ±103.86
CKMB (0.00- 24.0 U/L)	19.00 ±3.16	17.25 ±3.96	18.13 ±3.69	78.00 ±13.00	259.83 ±345.28	223.46 ±317.33	93.58 ±94.25	129.45 ±160.86	121.17 ±148.94
Leptin (pg/mL)	1.17 ±0.54	0.63 ±0.12	0.90 ±0.48	1.50 ±1.28	0.95 ±0.75	1.06 ±0.91	1.96 ±0.80	0.89 ±0.57	1.13 ±0.77
Resistin (ng/mL)	1.86 ±0.97	2.72 ±1.71	2.29 ±1.46	4.28 ±1.16	7.11 ±3.18	6.54 ±3.11	3.81 ±2.81	2.86 ±2.50	3.08 ±2.60
Insulin (IU/mL)	1.64 ±9.84	32.50 ±54.17	17.07 ±41.87	1.25 ±0.06	3.61 ±14.39	3.14 ±12.91	21.52 ±33.02	13.78 ±19.35	15.56 ±23.46

BMI- body mass index, TG- triglycerides, CHOL- cholesterol, Tropo I- Troponin I, CKMB- creatine kinase MB, data were expressed as the mean ±SD.

at room temperature for 2 hrs in the case of leptin and at 37 °C for 1 hr in the case of resistin. The solution was decanted, and the wells were washed 4 times. 100 μl Streptavidin-HRP working solution was added to each well except the chromogen blank. The plate was sealed with the plate cover and incubated at room temperature for 30 minutes in case of leptin. However, the plates were incubated for 1 hr at 37 °C in case of resistin. The solution was decanted, and the wells were washed 4 times. Later, 100 μl was added to each well from Stabilized Chromogen. The plates were incubated for 30 min in the dark at room temperature. 100 μl of stop solution was added to each well. The plate was gently tapped on one side to mix. The color of the solution in the wells changes from blue to yellow. Finally, the absorbance of each well was read at 450 nm against the blank.

Statistical analysis

Data were expressed as the mean ± SD. The parameters were analyzed statistically using the program GraphPad Prism. The student's t-test was used to compare any variations observed between experimental and control groups. The one-way ANOVA was used to determine whether there were any statistically significant differences between the two groups compared to the control. The Pearson correlation coefficient examined the relationship between leptin/resistin concentration and the analyzed parameters against different BMI. Statistical significance was set at a p-value of less than 0.05. P values were indicated by *: (*) <0.05, (**) <0.01, (***) <0.001, (***), <0.0001(****).

Results

Fast and accurate identification of AMI may lower fatality rates throughout the globe. Subsequently, cell loss in the myocardium raises the biochemical biomarker levels (25). The importance of adipocyte-derived polypeptide hormones like leptin and resistin in metabolic regulation has been extensively demonstrated (8,26). Despite medical advances in CVD treatment, patients with T2DM continue to be at higher risk (27). The present study evaluated the relationship between resistin and leptin levels with obesity and CAD risk factors, including AMI with hypoxia conditions.

Demographic and serum biochemical parameters among the AMI subjects

The study included 62 patients diagnosed with AMI, of which 22.58% were female and 77.41 % were males. Among the selected subjects, 10 (16.13%) were with normal BMI (Group 2), and 52 (83.87%) were obese with varying BMI (Group 3). In addition, 15 healthy volunteers were considered in the study (Group 1). The demographic and serum biochemical parameters of subjects have been summarized in Table 1. The mean age of Group 2 and 3 subjects was significantly (p<0.05) higher than the control group. The mean weight was comparatively lesser in Group 2 than in the control, but Group 3 showed a higher weight. Serum glucose, HbA1C, TG, cTnI, CK-MB, leptin, and resistin were significantly (p<0.05) higher in groups 2 and 3 than in Group 1. In contrast, cholesterol and insulin showed (p<0.05) lesser content in groups 2 and 3 compared to the control.

Gender-related difference in BMI of study subjects

A t-test was performed to compare the gender-related difference in BMI of study subjects for each group. Compared to the control (Group 1), Group 3 females showed markedly higher BMI (t=2.656; df=14; p=0.0188*), however, the BMI of Group 1 and 2 were comparable (t=0.666; df=4; p=0.54). Among AMI subjects (Group 2 and 3) BMI was not significantly different (t=2.345; df=12; p=0.037). Among males, the BMI of Group 2 was comparable with control (t=1.265; df=10; p=0.234). However, group 3 showed a significant difference (t=3.06; df=42; p=0.004*). AMI subjects in groups 2 and 3 also showed a significant difference (t=5.370; df=46; p=<0.0001****).

Association of BMI of study subjects with serum leptin level

Leptin levels were increased in patients with AMI subjects compared with control (healthy volunteers), i.e., Group 1 (1.06 ± 0.91 and 1.13 ± 0.77 vs. 0.9 ± 0.48), but the increase was not significantly different (p>0.05). Table 2 displays the statistical significance of leptin concentration between different groups. With respect to gender, there was no difference (p>0.05) between the leptin concentration of males and females in group 1 (r=0.74, p=0.139) and group 3 (r=0.044, p=0.511). Group 2 was not determined due to the lesser number of subjects. Figure 2 illustrates the association between serum leptin and BMI of study subjects. According to Pearson's correlation coefficient analysis, Groups 1 and 2 lacked an association between leptin and BMI (r=0.022, p=0.727 and r=0.196, p=0.199). In contrast, leptin levels in group 3 subjects showed a higher association with BMI (r=125, p=0.01)
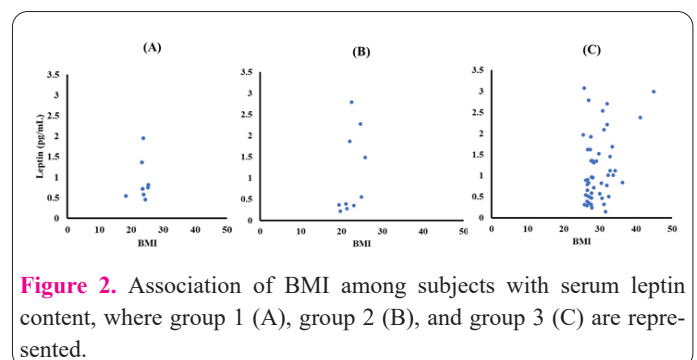
Figure 2. Association of BMI among subjects with serum leptin content, where group 1 (A), group 2 (B), and group 3 (C) are represented.

Table 2. A t-test performed between groups for leptin and resistin concentration.

Comparing Groups	Leptin	Resistin
Group 1 and 2	T=0.423; df=16; p=0.678	T=3.371,df=16, p=0.0039**
Group 1 and 3	T=0.826; df=58; p=0.412	T=0.8295,df=58, p=0.4102
Group 2 and 3	T=0.273; df=60; p=0.786	T=3.667,df=60, p=0.005***

df- degree of freedom; P values were indicated by *: (*) <0.05, (**) <0.01, (***) <0.001, (***), <0.0001(****).

Table 3. Pearson Correlation of BMI with leptin and resistin.

Groups	Leptin		Resistin	
	P-value	R-Squared	P-value	R-Squared
1	0.727	0.022	0.420	0.110
2	0.199	0.196	0.736	0.015
3	0.010*	0.125	0.759	0.001

P values were indicated by *: (*) <0.05, (**) <0.01, (***) <0.001, (***), <0.0001(****).

Table 4. Pearson Correlation of BMI with leptin and resistin level in male and female study subjects.

Group	Leptin vs. BMI		Resistin vs. BMI	
	Female	Male	Female	Male
1	R=0.24, p=0.50	R=0.02, p=0.857	R=0.012, p=0.891	R=0.944, p=0.0281
2	ND	R=0.255, p=0.201	ND	R=0.054, p=0.5788
3	R=0.044, p=0.511	R=0.23, p=0.0015**	R=0.016, p=0.69	R=0.0002,p=0.917

ND- not determined; P values were indicated by *: (*) <0.05, (**) <0.01, (***) <0.001, (***), <0.0001(****).

(Table 3). In Groups 1 and 2, no correlation was noticed between different gender and BMI, whereas in group 3, the male subject showed statistical correlation (r=0.23, p=0.0015**) (Table 4).
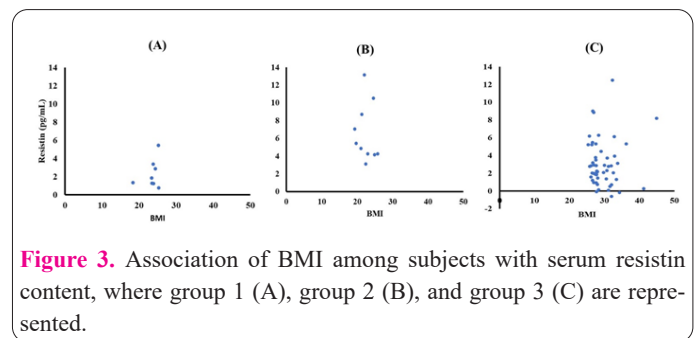
Association of BMI of study subjects with serum resistin level

Like leptin, the resistin level increased in AMI patients compared with control (6.54 ±3.11 and 3.08 ±2.60 vs. 2.29 ±1.46). Group 2 resistin level was significantly different (p=0.0039) than the control (group 1). Resistin levels in AMI patients also varied significantly (p=0.0005) (Table 2). With respect to gender, there was no difference (p>0.05) between the resistin concentration of males and females in group 1 (r=0.010, p=0.898) and group 3 (r=0.061, p=0.43). Group 2 was not determined due to the lesser number of subjects. Figure 3 illustrates the association between serum resistin and BMI of study subjects. Pearson's correlation coefficient analysis revealed a lack of association between resistin and BMI in all the groups (Table 3). Groups 2 and 3 showed a lack of correlations between different gender and BMI. However, males in group 1 showed a significant correlation (r=0.944; p=0.0281) (Table 4).

Discussion

Fast and accurate identification of AMI may lower fatality rates throughout the globe. Subsequently, cell loss in the myocardium raises the biochemical biomarker levels (25). The importance of adipocyte-derived polypeptide hormones like leptin and resistin in metabolic regulation has been extensively demonstrated (8,26). Despite medical advances in CVD treatment, patients with T2DM continue to be at higher risk (27). The present study evaluated the relationship between resistin and leptin levels with obesity and CAD risk factors, including AMI with hypoxia conditions.

A study by Ali et al. suggested that AMI development is associated with T2DM, smoking, obesity, advanced age, and hypertension (28). Our results showed significantly lower values for cholesterol and insulin and lower levels of HbA1C in AMI subjects with normal BMI and varying BMI, suggesting an important role of dyslipidemia and hyperglycemia in the studied hypoxia patients (29,30). Stu-

Figure 3. Association of BMI among subjects with serum resistin content, where group 1 (A), group 2 (B), and group 3 (C) are represented.

dies suggested that CK-MB, cTnI, and C-reactive protein were used as cardiac biomarkers to assess AMI (31,32). cTnI has a high sensitivity for detecting CVD-related conditions. Therefore, it is often used as a diagnostic marker for AMI (33). In the current study, cardiac biomarkers were elevated in the groups of AMI with normal BMI and AMI with varying BMI. Cardiac and diabetic biomarkers were used in our study because they are easy to obtain and can be related to the indices we used.

Additionally, body compositional disparities between the sexes must be considered. Women have a larger proportion of fat mass than males of the same BMI (34). The metabolic syndrome, obesity, and CVD may be worsened by excessive visceral fat, although femoral-gluteal fat may act as a "sink" for lipids (35). The current study noticed gender-related disparities between males with AMI and those with AMI with varying BMI groups. According to our study, only group 3 subjects had a significant difference in BMI between males and females. According to Milcent et al. (36), one-third of the disparities in coronary intervention utilization can be attributed to a gender discrepancy. However, age and comorbidities account for two-thirds of the same study. In an analysis of many patients, the authors demonstrated that women with an AMI had a higher mortality rate (37). However, our findings must be supported by large-scale prospective multicenter trials with a rational design to gender disparities in AMIs with varying BMI.

To reduce the risk of CVD in diabetics, new biomarkers for the early detection of the disease are desperately required. Serum resistin and leptin are well-documented risk factors for CVD disease in the general obese population (5,38,39). Also, leptin concentrations are elevated

in obese individuals due to their increased mass of adipose tissue and act as a mediator in human atherosclerotic conditions (3,40). Wallace et al. (41) noticed increased leptin levels with high BMI, triglycerides, blood glucose, and C-reactive protein.

Limitations of the study

The current study concluded that leptin levels significantly differed between patients with AMI with varying BMI and without correlation with gender. In the AMI group, Syed et al. (15) showed that leptin levels were substantially higher than those in the non-AMI group (11.23±3.12). Further, leptin levels may be linked to obesity and BMI, previously connected with a greater risk of CVD, like the AMI condition (10). A meta-analysis study by Zhang et al. (18) noticed elevated resistin levels in the AMI group compared with normal controls. Resistin levels were linked to insulin resistance, obstructive sleep apnea, and obesity (42,43). We hypothesize that the AMI patients in intermittent hypoxia stimulate the expression of resistin and leptin, as hypoxia stimulates the nuclear factor-κB pathway (44-46). Our results differed from those of Yaturu et al. (47), who found no connection between CAD patients and serum resistin, and differed from those of the control group.

Overall, a positive association between serum glucose, HbA1C, triglycerides, cTnI, CK-MB, leptin, and resistin in AMI patients was noticed. The study adequately demonstrated the significance and difference between groups with AMI and without AMI and between gender. Pearson's correlation of BMI with leptin level indicates a positive correlation in group 3 subjects but no correlation with Groups 1 and 2. Leptin levels of males in Group 3 had a higher correlation with BMI than females, and resistin levels showed a lack of correlations with BMI in all three groups. The present cross-sectional study on the physiology of serum leptin and resistin level in AMI and non-AMI did not support that circulating leptin concentration plays a critical role in AMI. However, the resistin level was significantly higher in obese AMI patients under the hypoxia effect. Further *ex vivo* or *in vivo* studies are required to confirm the effects of hypoxia on leptin and resistin synthesis.

Acknowledgments

Declaration of competing interest

The authors declare no competing financial interests.

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