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Resistin and prooxidant-antioxidant balance: Markers to discriminate acute coronary syndrome from stable angina

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Original Article

Abstract

BACKGROUND: Resistin and oxidative stress may play a role in the pathogenesis of coronary heart disease (CHD) including acute coronary syndrome (ACS). The aim of this study was to investigate the role of serum resistin and prooxidant-antioxidant balance (PAB) in ACS occurrence in order to differentiate it from stable angina. Moreover, we aimed to determine the correlation between resistin and PAB in patients with ACS and its difference from patients with stable CHD.

METHODS: This cross-sectional, descriptive study was conducted on 50 patients with ACS and 50 patients with stable CHD who underwent coronary angiography (CAG). Serum resistin level was measured using enzyme-linked immunosorbent assay (ELISA). PAB and other variables were analyzed using standard methods.

RESULTS: A significant increase in serum resistin and PAB was observed in patients with ACS (2.55 ± 0.13 ng/ml and 123.5 ± 5.58 HK unit, respectively) compared to patients with stable CHD (1.53 ± 0.12 ng/ml and 95.9 ± 2.7 HK unit, respectively) (P < 0.001). In addition, a significant positive correlation was seen between serum resistin and PAB in patients with ACS (r = 0.39; P = 0.005), but this correlation was not found in patients with stable CHD (r = 0.21; P = 0.140). Resistin (r = 0.52; P < 0.001) and PAB (r = 0.55; P < 0.001) were significantly associated with high-sensitivity C-reactive protein (hs-CRP) in patients with ACS, but this association was not found in patients with stable CHD (resistin: r = 0.24; P = 0.090; PAB: r = -0.02: P = 0.910).

CONCLUSION: High serum resistin or PAB levels, and their association with the occurrence of ACS, can be used as a robust discriminating factor to differentiate ACS from stable CHD.

Keywords: Acute Coronary Syndrome; Resistin; Antioxidants

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Introduction

Cardiovascular disease (CVD) is among the main causes of mortality and disability, and is becoming the worldwide leading cause of death in 2020. It is believed that oxidative stress due to increased formation of reactive oxygen species (ROS) leads to the manifestation of CVD. However, we consider all factors that increase the reactivation of oxygen species and their derivatives, such as peroxynitrite and lipid peroxides, as risk factors of CVD. The most critical event in CVD is the acute coronary syndrome (or unstable CVD) which occurs due to thrombus formation within the lumen of coronary arteries at the site of ruptured or eroded atherosclerotic plaques.[1,2]

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Acute coronary syndrome (ACS) represents a complex phenotype involving the interplay between endothelial dysfunction, pro-inflammatory, and pro-thrombotic components, and is influenced by genetic and environmental factors. Symptoms range from stable angina to myocardial infarction (MI) due to coronary artery occlusion by vulnerable plaques. Recent studies have supported the role of oxidative stress and inflammation as significant risk factors for CVD.[2]

The activation of ROS and their derivatives leads to the depletion of antioxidant capacity of tissues, structural damage, and loss of high-energy phosphates in the myocardium. However, increased chemical reactions or inadequate antioxidant defense system results in oxidative stress.[2]

The imbalance between antioxidant defense and the production of pro-oxidants causes endothelial dysfunction which results in atherogenesis and plaque destabilization.[1,3-5]

From the molecular aspect, atherosclerosis is an inflammatory condition. Inflammation leads to both formation and rupture of plaque, which leads to acute ischemic CVDs including ACS.

ROS are thought to play a role in the pathophysiology of CVDs.[6,7] Prooxidant-antioxidant balance (PAB), which is an indicator of oxidative stress, is considered as a cardiovascular risk predictor that estimates the extent of oxidative stress. However, studies have shown that PAB values are associated with CHD.[8]

In fact, coronary artery inflammation and its associated oxidative stress, due to the accumulation of lipids, leads to the formation of arterial lesions called atheroma. Furthermore, a high level of lipid in the plasma activates the endothelium and increases the adhesion of immune cells to the endothelium, which results in endothelial dysfunction. Ultimately, chemotactic factors are released from ruptured atherosclerotic lesions, resulting in platelet aggregation and thrombosis of the coronary artery and ACS.[9,10]

Moreover, ACS itself activates the systemic inflammatory cascade to protect the body against injury caused by ischemia. Homeostatic imbalance of adipokines interfere with the rate of production and secretion of other cytokines during the ACS-activated inflammation.

Recent studies have focused on diagnosing markers of oxidative stress and prognostic factors of ACS. Although several researchers have demonstrated the association between various cytokines and CHD, the impact of ACS-activated inflammation on adipokines remains unknown in ACS patients.

Moreover, the epicardial adipose tissue (EAT) covers the surface of the heart. The adipokines secreted from EAT can be divided into anti-atherogenic (such as adiponectin) and proatherogenic adipokines (such as resistin and leptin). Resistin is the adipocytokine that worsens glucose tolerance and induces insulin resistance.[11,12] Follow-up studies have explained the role of resistin in inflammatory processes, insulin resistance, and atherosclerosis, but there remains questions in this regard.[13]

Resistin is exclusively expressed in peripheral blood monocytes and macrophages of atheromas. It is expressed in human peripheral blood mononuclear cells and involved in inflammatory reactions.[14,15]

Human resistin is also expressed and secreted exclusively from macrophages and bone marrow cells in atheromas, which affect endothelial function and induce vascular smooth muscle cell proliferation.[16,17] Lipopolysaccharide, interleukin-1, IL-6, and tumor necrosis factor-α can enhance the resistin mRNA expression in human peripheral blood monocytes.[18] Furthermore, recombinant human resistin can promote human endothelial cell activity by enhancing endothelin-1 release, expressions of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and monocyte chemoattractant protein-1.[19,20] It has been reported that resistin, secreted by macrophages infiltrating the atheroma, affects endothelial function and stimulates vascular smooth muscle cells migration.[17] Therefore, resistin plays a role in the development of atherosclerosis. Resistin is an adipocytokine and functions as a link between inflammation, metabolic disorder, and atherosclerosis. In humans, resistin is primarily a product of macrophages.[21,22] Resistin is highly expressed in human peripheral blood mononuclear cells and is involved in inflammatory reactions.[23] Resistin secreted by macrophages infiltrating the atheromas affects endothelial function and stimulates vascular smooth muscle cells migration.[13,17]

In chronic inflammatory conditions such as diabetes, obesity, and atherosclerotic CVD, proatherogenic imbalance is observed; this means the serum contains higher adiponectin levels and lower resistin and leptin levels. Therefore, it seems that ACS-activated inflammation must be categorized as an acute inflammation rather than a chronic inflammation.[24]

It has been hypothesized that resistin serum

level and PAB can predict ACS in patients with CHD. Several studies have reported the significant association between resistin serum level and ACS. In the present study, we assessed the possible association of resistin with high-sensitivity C-reactive protein (hs-CRP) as a marker of inflammation and other CVD risk factors.

Materials and Methods

In this cross-sectional descriptive study was conducted on 100 patients [50 patients with ACS and 50 patients with stable coronary artery disease (CAD)] aged between 44 and 86 years who underwent diagnostic coronary angiography (CAG) in Chamran Hospital in Isfahan, Iran, from May 2015 to January 2016. The subjects were selected from among patients who referred to the department of cardiology with a complaint of chest pain. The diagnosis was made according to the result of angiography, electrocardiogram, serum troponin level, and clinical findings. They were all admitted to the hospital between May 2015 and March 2016. Patients with inflammatory diseases (such as rheumatoid arthritis, lupus, vasculitis, pulmonary fibrosis, and retroperitoneal fibrosis), malignant diseases, impaired liver function, renal failure, uncontrolled diabetes, severe heart failure, and history of trauma and surgery were excluded from the study.

CAG was performed for all subjects through the femoral artery approach. Informed consent was obtained from all patients before enrollment. The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences (Project number: 395890) according to the principles of the Declaration of Helsinki.

Characteristics of patients and sample collection: Based on the definition, stenosis in more than 75% of any major coronary arteries or more than 50% of the left main coronary artery cross-sectional area is considered a significant CAD.[25,26]

All data including age, gender, serum creatinine, lipid profile [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG)], body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), tobacco use, medication history, hypertension (HTN; defined as systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg in two consecutive times or consumption of antihypertensive drugs), diabetes mellitus (DM; defined as a fasting blood glucose ≥ 126 mg/dl and hemoglobin A1C ≥ 6.5%, or use of hypoglycemic medication), and other risk factors of CHD were recorded.

Before angiography, venous blood samples were obtained from patients and placed in a serum separator tube. We let the tube stand for at least 20 minutes at room temperature. Then, the tube was centrifuged at 3000 G for 10 minutes and the obtained serum was liquated and stored at -80 °C until assayed.

Then, CAG was performed in all subjects through the radial or femoral artery approach. Two experienced cardiologists, who were unaware of the patient's clinical history and biochemical results, evaluated all angiograms.

Serum levels of blood sugar (BS), TG, TC, HDL-C, and LDL-C were measured via enzymatic methods by using commercial kits (Pars-Azmoon, Tehran, Iran) and an automated analyzer (Hitachi, Japan) according to the manufacturer's recommendations.

Using an immunoturbidimetric method and a commercial kit (Pars-Azmoon, Tehran, Iran) according to the manufacturer's recommendations, hs-CRP was measured. Cases with an elevated level of hs-CRP (above 3.0 mg/l) were also excluded to avoid the bias effect of an existing inflammation.

Resistin analysis using enzyme-linked immunosorbent assay: Enzyme-linked immunosorbent assay (ELISA) technique was used to evaluate serum resistin levels. This was measured with an enzyme immunoassay kit (Hangzhou East Biopharm Co. Ltd, China) according to the manufacturer's instructions. Subsequently, the standard curve was calculated using a linear regression equation, and the results were extracted for the samples.

Prooxidant-antioxidant balance assay: PAB assay was applied based on the method proposed by Pasterkamp et al.[27] In brief, the standard solutions were prepared from 0 to 100% by mixing 250 µM hydrogen peroxide with 3 mM uric acid in 10 mM NaOH. The TMB (3,3',5,5'-Tetramethylbenzidine) solution was prepared by dissolving a tablet of TMB in 10 ml substrate buffer (0.05 M acetate buffer; pH: 4.5). TMB cation was prepared by adding 18 µl of freshly-pure chloramine-T solution (10 mM) to 1 ml of the TMB solution. The TMB cation was incubated for 20 minutes at 37 °C and 1.25 units of peroxidase were added to 9 ml of the TMB solution (working solution).

In each well of a 96-well plate, 10 µl of each sample, standard or blank, was mixed with 200 µl of

working solution and incubated in a dark place at 37 °C for 12 minutes. Then, 100 µl of HCl (2N) was added to each well, and HCl was measured in an ELISA reader at 450 nm. A standard curve was provided for the values relative to the standard samples. The percentage of hydrogen peroxide in the standard solution was defined as arbitrary Hamidi-Koliakos (HK) units. The values of the PAB are expressed in arbitrary HK units. Based on the values obtained from the abovementioned standard curve, the values of the unknown samples were calculated.

Continuous normally distributed variables are presented as mean ± standard deviation (SD), and non-normally distributed variables are presented as median [interquartile range (IQR)]. Normality assumption was checked using Kolmogorov–Smirnov test. Two-tailed student's t-test was used to compare serum resistin level and the other variables between the two groups. To investigate the associations between serum resistin level and other variables, paired t-test and one sample sign test were used for normally and non-normally distributed variables, respectively. P-values of less than 0.05 were considered statistically significant. The statistical analyses were performed using SPSS software (Version 22, IBM Corporation, Armonk, NY, USA). The receiver operating characteristic (ROC) curve was used for illustrating the ability of PAB and resistin serum level in predicting the occurrence of ACS.

Continuous variables were compared between ACS and stable CAD groups using independent t-test. The Pearson correlation analysis was used to investigate the correlations between serum miR-21, visfatin, and other related variables.

Results

After primary evaluations, 50 patients were included in each of the groups (ACD and stable CHD). The mean ± standard error (SE) age of the participants was 63 ± 1.74 and 62 ± 1.26 years in the ACS and stable CHD groups, respectively (age range: 45-85). Clinical characteristics data of all subjects are summarized in table 1. The demographic characteristics of age, BMI, and blood pressure were not significantly different between the ACS and stable CHD groups. There were no significant differences in other cardiovascular risk factors, including cigarette smoking, LDL-C, TC, total TG, creatinine, and history of diabetes. The levels of serum HDL-C were significantly lower in the ACS group than the stable CHD group. Rates of current smoking were similar between the two groups ($P > 0.050$) (Table 1).

According to the data analysis, levels of serum inflammatory markers (hs-CRP) were significantly higher in the ACS group (2.1 ± 0.051 mg/l) than the stable CHD group (1.68 ± 0.052 mg/l) ($P < 0.001$).

The result of ELISA analyses showed that the mean serum resistin levels were significantly higher in patients with ACS (2.55 ± 0.13 ng/ml) than those with stable CHD (1.53 ± 0.12 ng/ml) ($P < 0.001$) (Figure 1a).

The result of PAB assay showed that the mean serum PAB value was significantly higher in patients with ACS (123.5 ± 5.58 HK unit) than in those with stable CHD (95.9 ± 2.7 HK unit) ($P < 0.001$) (Figure 1b). These results indicate that the PAB level was significantly elevated in the ACS group compared to the stable CHD group.

Table 1. Summary of data analysis in the acute coronary syndrome and stable coronary heart disease groups

Characteristics	Patients with ACS (n = 50)	Patients with stable CHD (n = 50)	P
Male gender [n (%)]	31 (19)	30 (20)	0.840
Age (year)	63.26 ± 1.74	62.32 ± 1.26	0.670
Systolic blood pressure (mm Hg)	133.75 ± 2.88	128.21 ± 1.91	0.115
Diastolic blood pressure (mm Hg)	81.23 ± 1.32	79.31 ± 0.74	0.207
BMI (kg/m^2)	24.48 ± 0.35	24.11 ± 0.31	0.413
Serum creatinine (mg/dl)	1.06 ± 0.029	1.01 ± 0.027	0.203
TC (mg/dl)	196.10 ± 3.87	195.70 ± 3.88	0.930
LDL-C (mg/dl)	128.38 ± 3.67	122.96 ± 3.98	0.280
HDL-C (mg/dl)	35.58 ± 5.02	40.60 ± 3.20	0.008
TG (mg/dl)	161.20 ± 6.02	160.32 ± 3.72	0.940
Glucose (mg/dl)	120.00 ± 2.34	124.70 ± 1.62	0.112
Hemoglobin A1c (%)	6.09 ± 0.088	6.23 ± 0.061	0.177

Normally distributed data are presented as mean ± [Standard error (SE)] or number (%). Two-tailed student's t-test was used to compare variables between the two groups. P-value < 0.050 was considered as a statistically significant association. ACS: Acute coronary syndrome; CHD: Coronary heart disease; BMI: Body mass index; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol; TG: Triglycerid

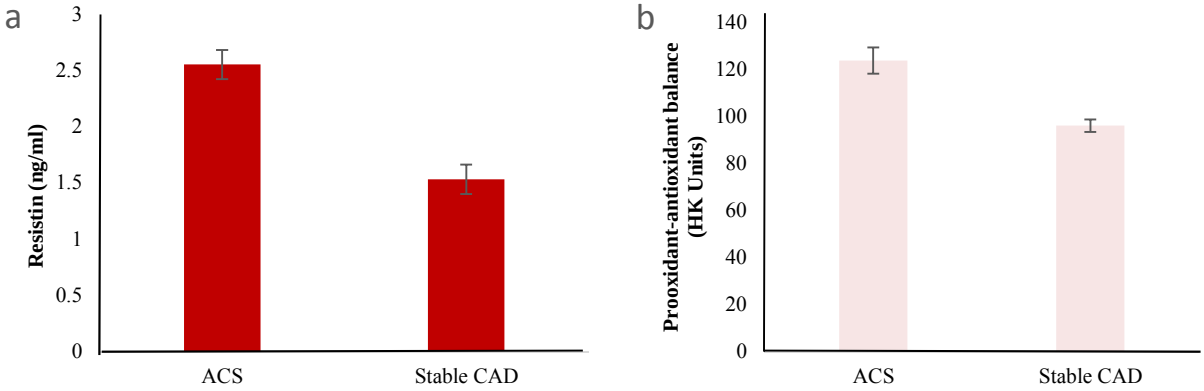

Figure 1. a. Serum resistin levels in patients with acute coronary syndrome and patients with stable coronary heart disease; b. The prooxidant-antioxidant balance value of patients with acute coronary syndrome and patients with stable coronary heart disease

There were significant differences between the resistin or prooxidant-antioxidant balance value of the patients with ACS and patients with stable CHD ($P < 0.001$ for both).

ACS: Acute coronary syndrome; CAD: coronary artery disease; CHD: Coronary heart disease

Illustrating the ability of resistin level and serum prooxidant-antioxidant balance level in predicting the occurrence of acute coronary syndrome

The ROC curve was used to help in discriminating ACS from stable CHD based on resistin and PAB serum levels. The area under the curve (AUC) demonstrates how the resistin and PAB serum levels can act as a prognostic factor of ACS.

Each point on the ROC curve also shows the sensitivity and specificity of these parameters in predicting ACS. ROC analysis provides 2 main outcomes, the diagnostic role of the test and the optimal cut-off point value for the test. Cut-off points dichotomize the test values, and this provides the diagnosis (diseased or not). The identification of the cut-off point value requires a simultaneous assessment of sensitivity and specificity.[28]

The ROC curve for serum resistin was analyzed to predict the occurrence of ACS (Figure 2).

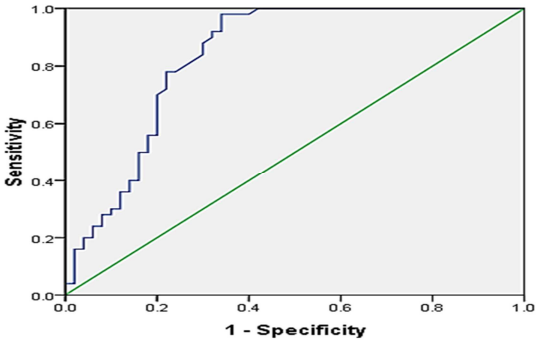

Figure 2. The receiver operating characteristic curve for serum resistin to differentiate acute coronary syndrome from stable coronary heart disease in the study population

The area under the ROC curve for resistin was 0.834 (95% CI: 0.750–0.918; $P < 0.001$). The cut-off point (maximal sensitivity and specificity) for resistin was 1.66 ng/ml (sensitivity: 78.00%; specificity: 76.00%).

Likewise, the ROC curve for serum PAB was analyzed to distinguish ACS from stable CHD (Figure 3).

The area under the ROC curve for PAB was 0.686 (95%CI: 0.577–0.794; $P < 0.001$). The cut-off point (maximal sensitivity and specificity) for PAB was 94.5 HK unite (sensitivity: 62.00%; specificity: 58.00%).

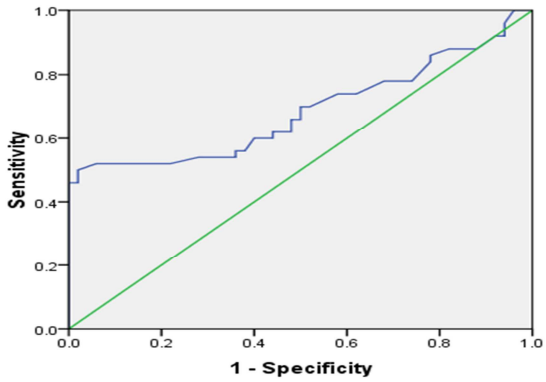

Figure 3. The receiver operating characteristic curve for serum prooxidant-antioxidant balance to distinguish acute coronary syndrome from stable coronary heart disease in the study population

Furthermore, the relationships between serum resistin level and other variables (including demographic variables, lipid profile, and other CVD risk factors) was assessed using the univariate analysis.

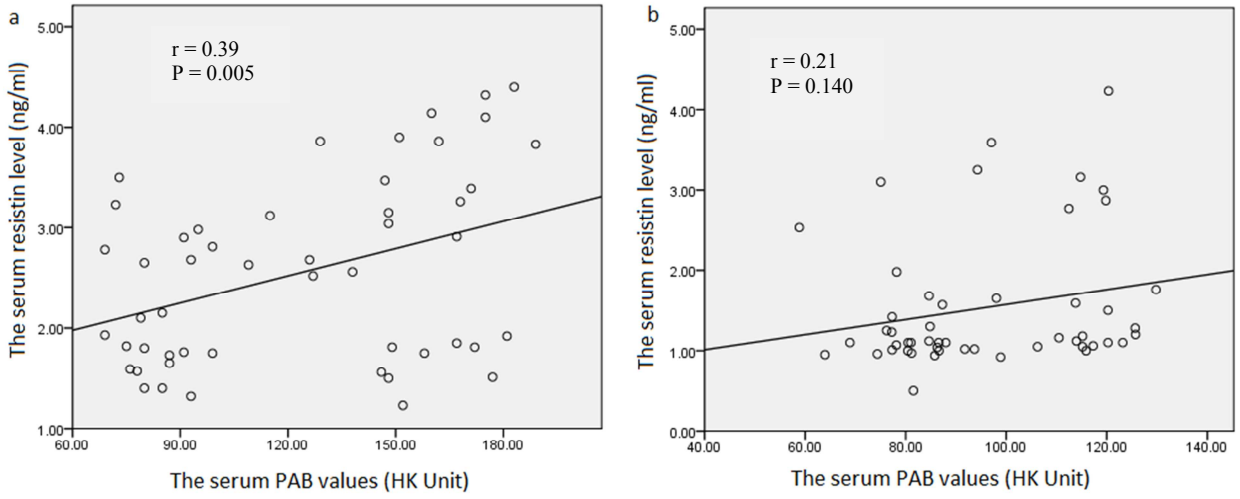

Figure 4. Correlation between serum resistin and prooxidant-antioxidant balance (PAP) in a. patients with acute coronary syndrome (r = 0.39; P = 0.005), and b. patients with stable coronary heart disease (r = 0.21; P = 0.140)

The serum resistin level showed no correlation with demographic variables such as age, BMI, and systolic and diastolic blood pressure. Moreover, serum resistin level showed a negative significant correlation with HDL-C (r = -0.259; P = 0.009), but showed no significant correlation with LDL-C, TC, and TG.

Correlation analysis showed that there was a significant correlation between serum resistin and PAB in patients with ACS (r = 0.39; P = 0.005), but this correlation was not found in patients with stable CHD (r = 0.21; P = 0.140) (Figure 4).

The data analysis also showed a highly significant positive correlation between serum resistin and hs-CRP levels (a serum inflammatory marker) in the ACS group (r = 0.52; P < 0.001), but this correlation was not found in the stable CHD group (r = 0.24; P = 0.090). Moreover, it showed a highly significant positive correlation between serum PAB values and hs-CRP level in the ACS group (r = 0.55; P < 0.001), but this correlation was not found in the stable CHD group (r = -0.02; P = 0.910).

In addition, we found a significant negative correlation between serum PAB values and HDL-C level (r = -0.278; P < 0.010) in the ACS group. Nevertheless, serum PAB value showed no significant correlation with LDL-C, TC, and TG levels.

Discussion

CVDs, including ACS, are among the major causes of morbidity and mortality worldwide. Acute coronary syndrome (ACS) is a multi-factorial disease, and hypercholesterolemia has been recognized as one of its major risk factors.[29] ACS severely threatens human health with increasing morbidity; therefore, early treatment of ACS might improve the adverse events of this disease.[30] The mechanism underlying ACS involves instability and rupture of atherosclerotic plaques, platelet aggregation, and thrombosis.[31] Instability of coronary plaque leads to progression of stable CAD to ACS.[31,32] Multiple biomarkers in the serum or plasma can provide appropriate diagnostic tools for this disease.

A particularly important contributing factor of the arterial plaque vulnerability and instability is inflammation.[33,34] Several factors are involved in inflammation and plaque instability, including adipocytokines and other various inflammatory and proinflammatory molecules.[35] MicroRNAs and adipocytokines is one of the key factors in plaque instability and the manifestation of ACS.

Adipocytokines and oxidative stress are considered as major risk factors for CHD.[6,36] Therefore, this study was designed to investigate the association between resistin serum level and PAB value. This association might help in discriminating ACS from stable CHD.

In the current study, we observed a higher serum resistin level in the ACS group compared to the stable CHD group. Figure 2 shows the cut-off values of resistin, which is associated with ACS.

The study by Qiao et al. showed that serum resistin level increased with inflammatory factors and myocardial impairment.[13] They suggested that human resistin might play an important role in the pathogenesis of atherosclerosis and acute myocardial infarction (AMI) as an inflammatory factor. This finding was in line with that of the

present study, which showed that serum resistin might play an important role in the pathogenesis of ACS. The cut-off point for resistin, as a predictor for ACS, was determined in the present study. We showed that serum resistin at the cut-off of 1.66 ng/ml yielded a sensitivity and specificity of 78% and 76%, respectively, in predicting the occurrence of ACS. The accuracy (AUC) for resistin was 0.834 (95% CI: 0.750–0.917; P < 0.001). These data show that resistin is an appropriate biomarker for predicting ACS. Verma et al. found that resistin may contribute to the atherosclerotic process by activation of endothelial cells thus leading to endothelial dysfunction and thereby the stimulation of multiple pro-atherosclerotic pathways.[37] However, the present study results indicated that serum resistin level can help in discriminating ACS from stable CHD, which is a demanding clinical finding.

We found higher serum PAB values in patients with ACS compared to those with stable CHD. The cut-off point of PAB for predicting ACS was determined using ROC (Figure 3).

Several studies have shown that oxidative stress plays a crucial role in the pathophysiology of atherosclerosis and CHD.[6,7] Environmental stress causes excessive production of reactive oxygen species (ROS), which leads to progressive oxidative damage. ROS acts as the initiator of oxidative cascade, which results in LDL oxidation, endothelial dysfunction, and vascular smooth muscle proliferation and migration.

In the present study, a significant correlation was found between PAB level and the risk of CVDs; thus, prooxidant-antioxidant imbalance is associated with atherosclerosis and CVD.[8,38] Ashok and Ali. also considered increased PAB value as a risk factor for ACD.[39]

In addition to the significant correlation of serum resistin level and PAB with hs-CRP, we found significantly higher values of both serum resistin and PAB in patients with ACS. We believe this correlation predicts the role of both variables among the markers of plaque formation through the inflammatory process.

In clinical practice, increase in inflammatory biomarkers and obesity are considered as prognosticators of cardiovascular events. Adipocytokines and other various inflammatory and proinflammatory molecules are involved in inflammation and plaque instability.[40] Hs-CRP represent the degree of the inflammatory response in the atheromatous plaque and is closely related to the instability of coronary artery plaque, which leads to the occurrence of ACS.

It has been demonstrated that inflammation and atherosclerosis play a key role in the pathogenesis of CVDs including the ACS.[41,42] According to the results of the current study, both resistin and PAB showed a negative significant correlation with HDL-C level, but showed no correlation with total lipid profile. Previous studies have reported similar results. Recent studies are in agreement with these findings. Chen et al.,[43] showed that resistin is negatively associated with HDL-C level in patients with metabolic syndrome. Similarly, Bednarska-Makaruk et al.[44] reported the association of adipokines with inflammatory markers and obesity in dementia. They found a negative correlation between resistin level mn and HDL. Various studies have shown that oxidative stress is negatively related to HDL-C level.[45,46] Not all studies support the present study findings. A few studies including the study performed by Rao and Kiran found no relationship between oxidative stress and HDL-C.[47]

In fact, the correlations of resistin and PAB values with the risk of ACS are evidence that ACS arises from an acute inflammatory condition. However, more studies must be performed to prove this finding and investigate the underlying metabolic pathways.

This reflected a complicated interaction between hs-CRP and resistin that may be through inflammatory mechanisms, given that ACS is an acute inflammatory condition. This finding may be indicative of a possible causal relationship between hs-CRP and resistin in patients with ACS. However, more studies are required to demonstrate this relationship and its metabolic pathways.

Limitations: This present study had a relatively small sample size, so we probably failed to detect a meaningful or obvious effect (lack of statistical power due to small sample size). Moreover, under small sample size conditions, a seemingly meaningful effect can occur by chance, but is not trustworthy. Because of these considerations, we recommend researchers to conduct similar studies with larger sample sizes to achieve more accurate results.

Conclusion

Resistin and PAB levels were found to have a significant correlation with the risk of ACS. Based on our findings, elevated resistin and PAB can both be predictors of the occurrence of ACS.

Furthermore, serum resistin level is highly correlated with PAB and both factors are highly correlated with hs-CRP, which is an inflammatory

marker. Thus, it can be concluded that resistin and PAB values play a crucial role in the pathogenesis of ACS through the inflammatory process.

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Conflict of Interests

Authors have no conflict of interests.

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