



## Original article

## Increased level of resistin predicts development of atrial fibrillation



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## ABSTRACT

**Background:** Resistin is a peptide hormone that is secreted from lipid cells and is linked to type-2 diabetes, obesity, and inflammation. Being an important adipocytokine, resistin was proven to play an important role in cardiovascular disease. We compared resistin levels in patients with and without atrial fibrillation (AF) to demonstrate the relationship between plasma resistin levels and AF.

**Method:** One hundred patients with AF and 58 control patients who were matched in terms of age, gender, and risk factors were included in the trial. Their clinical risk factors, biometric measurements, echocardiographic work up, biochemical parameters including resistin and high-sensitivity C-reactive protein (hs-CRP) levels were compared.

**Results:** In patients with AF, plasma resistin levels ( $7.34 \pm 1.63$  ng/mL vs  $6.67 \pm 1.14$  ng/mL;  $p = 0.003$ ) and hs-CRP levels ( $3.01 \pm 1.54$  mg/L vs  $2.16 \pm 1.28$  mg/L;  $p = 0.001$ ) were higher than control group. In subgroup analysis, resistin levels were significantly higher in patients with paroxysmal ( $7.59 \pm 1.57$  ng/mL;  $p = 0.032$ ) and persistent AF ( $7.73 \pm 1.60$  ng/mL;  $p = 0.006$ ), but not in patients with permanent AF subgroups ( $6.86 \pm 1.61$  ng/mL;  $p = 0.92$ ) compared to controls. However, hs-CRP levels were significantly higher only in permanent AF patients compared to control group ( $3.26 \pm 1.46$  mg/L vs  $2.16 \pm 1.28$  mg/L;  $p = 0.02$ ). In multivariate regression analysis using model adjusted for age, gender, body mass index, hypertension, diabetes mellitus, and creatinine levels, plasma resistin levels [odds ratio (OR): 1.30; 95% confidence interval (CI): 1.01–1.70;  $p = 0.04$ ] and hs-CRP levels (OR: 1.44; 95% CI: 1.12–1.86;  $p = 0.004$ ) were the only independent predictors of AF.

**Conclusion:** The elevated levels of plasma resistin were related to paroxysmal AF group and persistent AF group, but not to permanent AF group.

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## Introduction

Atrial fibrillation (AF) is the most commonly seen and treated arrhythmia in clinical practice [1]. In previous studies age, diabetes, hypertension, and cardiovascular diseases were proven to increase the risk of AF development [2]. Besides these, obesity directly or indirectly increases the risk of AF development [3]. Inflammation plays a leading role in the electrical and structural remodeling process in AF patients [4,5]. In a prospective study the basal C-reactive protein (CRP) levels were strongly and independently correlated with future AF development [6]. In addition, higher CRP levels were linked with the clinical severity of AF [7–9]. Interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$  were also found to be significantly high in AF patients [10]. These studies regarding inflammation

show its potential role in development, progression, and morbidity of the disease.

Resistin is a hormone that is abundantly secreted from the lipid cells and linked to type 2 diabetes and obesity. Obese people have a higher resistin level as compared to healthy ones and this correlates with body mass index (BMI) [11]. Studies done on patients who have inflammation proved that a correlation existed between resistin and inflammation markers [12].

Being an important adipocytokine secreted from lipid cells, resistin was proven to play an important role in cardiovascular disease. There are many trials conducted on various forms of coronary artery diseases. Reilly et al. proved that resistin levels were increased in parallel to other inflammatory markers and independently increased levels were correlated with increased coronary calcium scores determined by coronary computed tomography (CT) angiography [13]. Its importance as a marker of adverse cardiovascular event development was proven in studies conducted on patients with stable coronary artery disease [14–16]. In acute coronary syndrome patients, its prognostic effects on cardiovascular

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events and mortality were shown [17–20]. Resistin also plays a role in pathogenesis of heart failure and is associated with the prognosis [21–25].

Obesity and related diseases are important risk factors for AF [26]. As shown in clinical trials, resistin and adiponectin are related to certain AF risk factors such as inflammation, diabetes, obesity, myocardial infarction, and heart failure [20–23,27–30].

As resistin levels are increased in inflammation, diabetes, obesity, coronary artery disease, and heart failure, it raised a question of whether resistin and other pro-inflammatory adipocytokines secreted from the adipose tissue played a role in pathogenesis of AF. Adipocytokines may contribute to AF either directly or indirectly through risk factors or inflammation [31].

Based on the aforementioned data, in our study we compared plasma resistin levels of the patients listed below and its role in pathogenesis:

1. Those with and without AF
2. In three subgroups of AF which were paroxysmal, persistent, and permanent.

## Materials and methods

### Patient population

Our research was conducted between January 2011 and July 2012 in our tertiary reference center, Siyami Ersek Training and Research Hospital. We prospectively included 100 patients with AF who were admitted to our outpatient clinics. Patients signed informed consent forms upon entering. All patients' electrocardiogram (ECG) recordings were recorded and their previous ECG recordings were evaluated. All patients' age, gender, height, weight, waist circumference, current diseases, cardiovascular disease histories, family histories (regarding AF and CAD) were obtained and they were all evaluated for hypertension and diabetes. BMI was calculated using the formula weight (kg)/height (m)<sup>2</sup>. A detailed physical examination was performed.

AF was classified as paroxysmal when episodes were self-terminating and lasted no longer than 7 days. Persistent AF was defined as AF episodes lasting longer than 7 days or requiring termination by cardioversion. Patients with AF of  $\geq 6$  months in duration and  $\geq 1$  attempt of unsuccessful cardioversion to restore normal sinus rhythm were considered to have permanent AF. The patients were followed up for one year. Recurrence of AF was defined as readmission with symptoms of palpitation and an episode of AF was documented by ECG.

All of the study participants underwent two-dimensional and Doppler echocardiography by an experienced echocardiography specialist using a Vivid 3 (GE Healthcare Systems, Piscataway, NJ, USA) device. The systolic and diastolic diameters of the left ventricle, left atrial size, and volumes were measured. Left ventricular ejection fraction was calculated using the modified Simpson's method.

Patients with systolic heart failure (left ventricular ejection fraction <45%), heart failure with preserved ejection fraction, hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, congenital heart disease, acute coronary syndrome, valvular heart disease, post-operative AF, chronic liver/kidney disease, inflammatory or autoimmune diseases, malignancy, infection, unstable angina, and acute coronary syndrome were excluded from the trial.

### Biochemical analysis

A peripheral blood sample was collected into a 5 mL dry tube from all those who entered the research. They were centrifuged for 10 min at 1000  $\times$  g to get the serum. One of each patient's serum samples was kept at  $-20^{\circ}\text{C}$  until the biochemical analysis could detect resistin levels. Routine hemogram parameters [hemoglobin, hemotocrit, thrombocyte count, mean platelet volume (MPV), red blood cell dispersion width (RDW), blood glucose, urea, creatinine, sodium, potassium, CRP, aspartate aminotransferase, and alanine aminotransferase] were worked up.

Serum resistin levels were measured with the sandwich enzyme linked immunosorbent assay (ELISA) method which includes the binding of resistin in the samples to antibodies in solid microplate wells followed by the addition of anti-human resistin antibodies conjugated with biotin. The result was multiplied by 20, which is the dilution coefficient. Human resistin ELISA kit (Adipo-bioscience, Santa Clara, CA, USA) was used for the measurement. The normal range was 4–16 ng/mL.

Fifty-eight individuals who were matched in age, gender, and conventional risk factors and had normal findings in physical and echocardiographic examination were recruited as the control group. The study was approved by the institutional ethics committee.

### Statistical analysis

All data are presented as mean  $\pm$  SD or median (interquartile range) for parametric variables and as percentages for categorical variables. Continuous variables were checked for the normal distribution assumption using the Kolmogorov–Smirnov statistics. Differences between AF subgroups and control subjects were evaluated using the Kolmogorov–Smirnov test or ANOVA with the Tukey's post hoc test as appropriate. Categorical variables were tested by Pearson's  $\chi^2$  test and Fisher's exact test. The correlations between single variables were evaluated with Pearson or Spearman correlation tests. Forward stepwise multivariate logistic regression models were created to identify the independent predictors of AF. Variables with a  $p$ -value <0.10 in univariate analysis were included in the multivariate model. A  $p$ -value <0.05 was considered statistically significant. All statistical studies were carried out using Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, IL, USA).

## Results

The study population consisted of 100 patients with AF (paroxysmal AF 28 cases; persistent AF 32 cases; permanent AF 40 cases) (mean age  $60.7 \pm 11.7$  years) and 58 controls (mean age  $57.7 \pm 11.1$  years). The clinical and laboratory parameters were compared within the AF subgroups and between the AF and the control group and are reported in Table 1. Control subjects were matched to AF patients on the basis of age, gender, body mass index, measured blood pressure, and prevalence of hypertension, diabetes mellitus, and smoking. Patients with permanent AF were older, had higher rates of hypertension, and had reduced left ventricular ejection fraction compared to paroxysmal and persistent AF subgroups. BMI and systolic/diastolic blood pressure measurements were similar between the AF subgroups. The rate of beta blocker use was significantly higher in patients with AF compared to the control group ( $p=0.01$ ), but was similar within the AF subgroups ( $p=0.65$ ). The rate of recurrence was  $3.4 \pm 1.4$  episodes/year in paroxysmal AF and  $3.2 \pm 1.2$  episodes/year in persistent AF patients.

Resistin and hs-CRP levels were significantly higher in AF patients compared to the control group ( $7.34 \pm 1.63$  ng/mL

**Table 1**  
Clinical and demographic properties of control group and patients with atrial fibrillation.

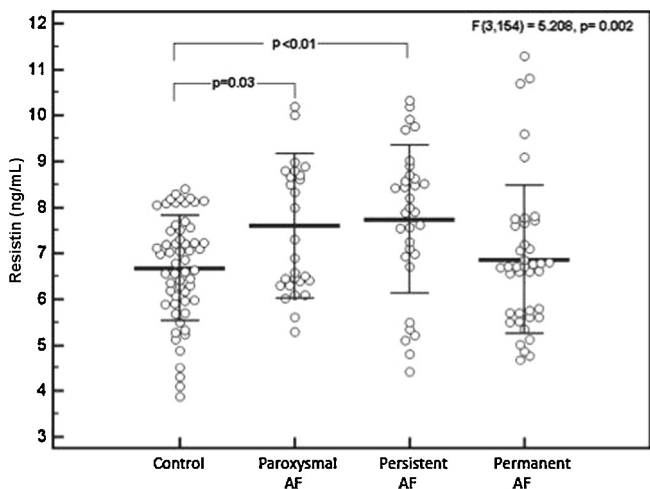
	Atrial fibrillation group (n = 100)			Control group (n = 58)	p*	p**
	Paroxysmal AF (n = 28)	Persistent AF (n = 32)	Permanent AF (n = 40)			
Age (years)	56.6 ± 14.8	60.1 ± 10.7	64.1 ± 9.1	57.7 ± 11.1	0.04	0.11
Male gender (%)	13(46.4)	13(40.6)	12(30)	28(48.3)	0.36	0.20
Body mass index (kg/m <sup>2</sup> )	28.5 ± 3.8	28.9 ± 4.3	27.1 ± 5.2	28.3 ± 4.1	0.22	0.71
Hypertension (%)	13(46.4)	22(68.7)	34(85)	35(60.4)	0.01	0.27
Diabetes mellitus (%)	8(28.6)	7(21.8)	10(25)	15(25.9)	0.84	0.90
Hyperlipidemia (%)	8(28.6)	8(25)	9(22.5)	20(34.5)	0.85	0.20
Current smoker (%)	5(17.9)	8(25)	7(17.5)	24(41.4)	0.55	0.16
Left ventricular EF %	55.9 ± 7.4	59.2 ± 5.7	52.2 ± 6.6	57.3 ± 6.9	0.01	0.11
Systolic BP (mmHg)	132.1 ± 26.5	129.6 ± 24.7	128.7 ± 33.1	127.7 ± 18.4	0.89	0.56
Diastolic BP (mmHg)	72.4 ± 18.5	71.3 ± 14.9	71.6 ± 14.6	75.1 ± 12.1	0.95	0.15
Paroxysms/year	3.4 ± 1.4	3.2 ± 1.2	–	–	NA	NA
<b>Medical treatment</b>						
Aspirin (%)	23(82.1)	20(62.5)	2(5)	25(43.1)	0.01	0.79
Warfarin (%)	5(17.9)	12(37.5)	38(95)	–	0.01	NA
RAS blocker (%)	13(46.4)	16(50)	25(62.5)	26(44.8)	0.36	0.27
Calcium channel blocker (%)	3(10.7)	12(37.5)	9(22.5)	10(17.2)	0.05	0.32
Beta blocker (%)	20(71.4)	19(59.4)	26(65)	21(36.2)	0.65	0.01
Antiarrhythmic drugs (%)	1(3.5)	2(6.2)	2(5)	–	0.90	NA

AF, atrial fibrillation; BP, blood pressure; RAS, renin–angiotensin system; NA, not applicable.

\* Comparison between atrial fibrillation subgroups namely paroxysmal, persistent and permanent atrial fibrillation.

\*\* Comparison between the control and atrial fibrillation groups.

vs  $6.67 \pm 1.14$  ng/mL;  $p = 0.003$  and  $3.01 \pm 1.54$  mg/L vs  $2.16 \pm 1.28$  mg/L;  $p = 0.001$ , respectively). In subgroup analysis, resistin levels were significantly higher only in patients with paroxysmal ( $7.59 \pm 1.57$  ng/mL;  $p = 0.032$ ) and persistent AF ( $7.73 \pm 1.60$  ng/mL;  $p = 0.006$ ) compared to controls (Fig. 1). Resistin



**Fig. 1.** Distribution of resistin levels in controls and patient subgroups stratified on the basis of the type of AF. Middle line: mean; thin lines:  $\pm 1$  standard deviation. AF, atrial fibrillation.

**Table 2**  
Comparison of laboratory parameters in AF subgroups and control subjects.

	Paroxysmal AF (n = 28)	Persistent AF (n = 32)	Permanent AF (n = 40)	Control (n = 58)	p*	p**
Hemoglobin (g/dL)	13.2 ± 2.3	13.8 ± 1.5	13.1 ± 1.8	13.4 ± 1.6	0.21	0.77
WBC count ( $10^3/\mu\text{L}$ )	9.1 ± 3.5	8.1 ± 2.1	7.8 ± 2.3	9.2 ± 3.8	0.14	0.08
Platelet ( $10^3/\mu\text{L}$ )	246.1 ± 68.1	259.7 ± 71.7	233.9 ± 59.6	243.8 ± 71.8	0.26	0.88
Fasting glucose (mg/dL)	100.1 ± 11.3	101.2 ± 9.2	98.5 ± 12.6	97.6 ± 16.7	0.61	0.32
Creatinine (mg/dL)	0.98 ± 0.41	0.88 ± 0.15	0.89 ± 0.30	0.84 ± 0.31	0.36	0.15
hs-CRP (mg/L)	2.80 ± 1.71	2.84 ± 1.49	3.26 ± 1.46	2.16 ± 1.28	0.39	0.001
Resistin (ng/mL)	7.59 ± 1.57	7.73 ± 1.60	6.86 ± 1.61	6.67 ± 1.14	0.05	0.003

AF, atrial fibrillation; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein.

\* Comparison between atrial fibrillation subgroups namely paroxysmal, persistent, and permanent atrial fibrillation.

\*\* Comparison between the control and atrial fibrillation groups.

levels in permanent AF patients were significantly lower than in patients with paroxysmal/persistent AF patients ( $p = 0.05$ ) and were similar to the control group ( $p = 0.92$ ). Whereas, only permanent AF patients had significantly higher levels of hs-CRP compared to the control group ( $3.26 \pm 1.46$  mg/L vs  $2.16 \pm 1.28$  mg/L;  $p = 0.002$ ). In patients with paroxysmal and persistent AF the CRP levels ( $2.80 \pm 1.71$  mg/L and  $2.84 \pm 1.49$  mg/L, respectively) were not statistically higher than controls (Table 2).

Laboratory and clinical parameters were compared in paroxysmal/persistent AF patients grouped according to the rate of AF recurrence. In patients with  $\geq 4$  episodes/year age, BMI, fasting blood glucose, creatinine, resistin ( $1.76 \pm 0.32$  ng/mL vs  $1.39 \pm 0.25$  ng/mL, respectively;  $p = 0.35$ ), and hs-CRP levels ( $2.75 \pm 1.71$  mg/L vs  $2.89 \pm 1.48$  mg/L, respectively;  $p = 0.73$ ) were not statistically different from patients with  $\leq 3$  episodes/year.

In the study population, resistin levels were correlated with CRP ( $r = 0.16$ ;  $p = 0.04$ ), creatinine ( $r = 0.26$ ;  $p = 0.01$ ), and fasting plasma glucose ( $r = 0.16$ ;  $p = 0.04$ ) levels. C-reactive protein levels were also correlated with plasma creatinine levels ( $r = 0.18$ ;  $p = 0.02$ ). Significant correlation of resistin and CRP levels with other parameters including rate of AF recurrence were not established.

In multivariate regression analysis using model adjusted for age, gender, BMI, hypertension, diabetes mellitus, and creatinine levels, plasma resistin levels [odds ratio (OR): 1.30; 95% confidence interval (CI): 1.01–1.70;  $p = 0.04$ ] and hs-CRP levels (OR: 1.44; 95% CI: 1.12–1.86;  $p = 0.004$ ) were the only independent predictors of AF.

## Discussion

The main finding of this study is that resistin levels are increased in AF patients compared to controls. In addition, resistin levels are correlated with hs-CRP levels which may indicate the role of inflammation in AF.

Resistin is an adipocytokine which is secreted from lipid cells and has been shown to be associated with obesity. The resistin levels are higher in obese individuals as compared to individuals of normal weight and this correlates with BMI [11]. Studies done on patients who have inflammation proved that a correlation existed between resistin and inflammation markers. On a cellular level, resistin seems to activate proinflammatory cytokines to create a potent proinflammatory effect [32].

Resistin's potential role in the cardiovascular disease process have been shown in various trials. It is an important marker in stable coronary artery disease, acute coronary syndromes, heart failure, and it is also associated with prognosis [13–25].

AF is associated with inflammation, diabetes, obesity, coronary artery disease, and heart failure which are associated with increased resistin levels, and other pro-inflammatory adipocytokines secreted from the adipose tissue that may contribute to AF either directly or indirectly through risk factors or inflammation [31]. The inflammation triggers an electrical and structural remodeling process in AF patients [4,5]. Frustaci et al. detected histological changes indicating inflammation in the atrial tissue [33]. Adiponectin is another important adipocytokine secreted from lipid cells. In a study conducted with adiponectin, when compared with a control group, plasma adiponectin levels were found to be linked to persistent AF but not paroxysmal AF. In this trial, increased collagen products were shown to increase in paroxysmal and persistent groups in relation to atrial remodeling and fibrosis [34]. In our study, we included permanent AF patients as well. Being related to obesity and inflammation, two factors that play an important role in AF pathogenesis, the marker resistin was found significantly higher in the patient group as compared to the control group. The same was true for paroxysmal and persistent subtypes, as well. Although the resistin levels were higher in permanent AF than in control group, it was not of statistical significance. One may conclude that the inflammatory marker secreted from adipose tissue, resistin, and atrial inflammation bear importance in patients without AF during transition to paroxysmal and persistent AF. A growing body of evidence suggests a possible association between inflammation and permanent atrial fibrillation, but inflammatory reaction might be of low-grade that resistin secretion could not reach statistical significance in comparison to control patients. However, CRP levels in the permanent AF group were significantly higher than controls in our study. Some previous papers reported statistically insignificant higher CRP levels in patients with permanent lone AF, and suggested a link between a low-grade inflammatory reaction and long-lasting AF [10,35,36]. Nevertheless, CRP levels were found significant in those with comorbidities and permanent AF [6,7]. We thought that comorbidities in our permanent AF group aggravated existing low-grade inflammation resulting in high CRP levels but not resistin. The evidence of resistin levels in permanent lone AF and none-lone AF compared to controls is lacking. Large-scale randomized trials are needed to precisely evaluate this issue. If our results were confirmed with large-scale studies, we assume that this issue may help clinicians differentiate the type of AF in asymptomatic patients. The differentiation of AF by itself may guide clinicians in choosing rhythm control or rate control strategy; if an asymptomatic AF patient has a high resistin level one may suppose that it might be converted to sinus rhythm. In our study, CRP and resistin proved to be independent risk factors for AF development in the multivariate analysis and its increase in conjunction with CRP also supports its role in the pathophysiology of the disease.

Two trials have been conducted on resistin and AF recently. As a substudy of the Framingham trial, the basal resistin levels were measured in 2487 individuals who did not have AF. They were followed up for 10 years for AF development. In this study, plasma resistin and CRP levels were found to correlate with AF development [31]. It was also determined that CRP and resistin levels were significantly correlated but when CRP was added to resistin, its effect decreased in multivariate analyses. Similar to this one, our results also suggested that CRP and resistin levels were increased parallelly and were related to AF in multivariate analyses. In Gungor et al.'s study from Turkey [37], the post-operative plasma resistin levels were found to be important in predicting post-operative AF development in 40 coronary artery bypass graft patients. Inflammation's role in post-operative AF development may explain the increase in resistin levels in this group of patients.

## Conclusion

As a result, we found that plasma resistin levels were higher in AF patients when compared to the control group and that they differed by the type of disease; patients with paroxysmal and persistent form of AF have significantly higher resistin levels while it was insignificant in permanent AF patients compared to control group. Our study, like other studies in the literature, supports resistin's potential role in AF and cardiovascular disease processes. More extensive studies are required to fully understand the relationship between adipocytokines and AF.

## Limitations

We only measured resistin levels in our study, not adiponectin or other adipocytokines. It is a cross-sectional study and the patient number is not high. It is also conducted in a single center. As we excluded more types of comorbidities that are often associated with AF, our study cannot be generalized to all AF patients.

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