Journal of Cardiology 63 (2014) 308–312

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Increased level of resistin predicts development of atrial fibrillation

Kazım Serhan Özcan (MD), Barış Güngör (MD)*, Servet Altay (MD), Damirbek Osmonov (MD), Ahmet Ekmekçi (MD), Fatma Özpamuk (MD), Tuğba Kemaloğlu (MD), Aydın Yıldırım (MD), Gülşah Tayyareci (MD), İzzet Erdinler (MD)

Department of Cardiology, Siyami Ersek Cardiovascular and Thoracic Surgery Center, 34087, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 18 March 2013
Received in revised form 10 October 2013
Accepted 18 October 2013
Available online 20 November 2013

Keywords:
Atrial fibrillation
Inflammation
Adipocytokines
Resistin

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 ± 1.63 ng/mL vs 6.67 ± 1.14 ng/mL; $p = 0.003$) and hs-CRP levels (3.01 ± 1.54 mg/L vs 2.16 ± 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 ± 1.57 ng/mL; $p = 0.032$) and persistent AF (7.73 ± 1.60 ng/mL; $p = 0.006$), but not in patients with permanent AF subgroups (6.86 ± 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 ± 1.46 mg/L vs 2.16 ± 1.28 mg/L; $p = 0.02$). In multivariate regression analysis using model adjusted for age, gender, body mas 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.

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)-α 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 adipocytokinine 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

* Corresponding author at: Siyami Ersek Hastanesi, Tıbbiye Caddesi, Üsküdar, Istanbul, Turkey. Tel.: +90 532 6742429/216 545 47 36; fax: +90 216 3379719.
E-mail address: drbarisgungor@gmail.com (B. Güngör).

0914-5087/$ – see front matter © 2013 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jjcc.2013.10.008

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 $(m)^2$. 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, malignity, 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 $-20\,^{\circ}C$ 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 χ^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