CLINICAL INVESTIGATION

A Preliminary Comparative Assessment of Apelin Serum Levels in Persistent Atrial Fibrillation and Coronary Artery Disease

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ABSTRACT

Background: Apelin, the endogenous ligand of orphan receptor APJ (gene symbol APLNR), is an adipokine that was suggested to have a direct correlation with obesity. This peptide might play a role in obesity-related disorders, especially in cardiovascular system. Currently, few data are available on levels and potential metabolic functions of apelin in different cardiac diseases including atrial fibrillation (AF) and coronary artery disease (CAD), which have common underlying pathophysiological mechanisms. This study aimed to investigate apelin levels in patients with AF and CAD that were overweight or obese, as well as its relationship with anthropometry and metabolic profile.

Methods: This preliminary investigation was compromised of 41 patients with AF and 39 with CAD aged $>$ 50 years and body mass index (BMI) $>$ 25 kg/m^2. Serum levels of apelin, fasting plasma glucose, insulin, homeostatic model assessment, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and very-low-density lipoprotein were measured.

Results: The apelin serum levels were not statistically different between patients with AF and CAD. A negative correlation was observed between apelin with weight ($r = -0.257$, $P = 0.023$) and BMI ($r = -0.258$, $P = 0.023$). Moreover, apelin showed an inverse correlation with insulin ($r = -0.227$, $P = 0.045$) and marginally with homeostatic model assessment ($r = -0.21$, $P = 0.066$). There was a negative association between apelin and triglyceride ($r = -0.238$, $P = 0.036$) and very-low-density lipoprotein ($r = -0.25$, $P = 0.027$).

Conclusions: Apelin serum levels were not significantly different among patients with AF and CAD. The unexpected inverse correlation of apelin with weight and BMI might indicate the dominant effects of pathophysiological conditions such as AF and CAD on serum levels of apelin compared with BMI and adipose tissue. Understanding the precise role of apelin in modulating obesity-induced disorders including AF and CAD requires further studies.

Key Indexing Terms: Apelin; Atrial fibrillation (AF); Coronary artery disease (CAD); Obesity; Overweight. **[Am J Med Sci 2016;▮(▮):▮▮▮–▮▮▮.]**

INTRODUCTION

Apelin, the endogenous ligand of orphan receptor APJ, is an adipokine that was extracted from bovine stomach for the first time.[1] This bioactive peptide is expressed by several tissues including brain, lung, heart, gastrointestinal tract, pancreas and adipose tissue in rodents and humans.[2,3] According to most studies, apelin gene expression increases during obesity and weight gain and seems to be involved in obesity-related metabolic disorders.[4,5] Apelin has been proposed to play a critical role in the cardiovascular system. Its potential mechanisms of action include stimulating heart rate, contractility and propagation of action potential,[6-8] vasodilatation via nitric oxide pathway[9] and involvement in the regulation of vascular tone through inhibiting the electrical activity of vasopressin-releasing neurons.[10] Moreover, Apelin-APJ system might play a key role in the endothelial oxidative stress and atherosclerotic plaques formation.[11] Previous studies also demonstrated the probable role of apelin in insulin resistance and glucose utilization.[12,13] However, there are few studies that have investigated the levels and potential metabolic functions of apelin in different heart disorders currently.

Atrial fibrillation (AF) is the most common arrhythmic disabling disorder. The prevalence of AF is increasing because of aging of the population and seems to be a major health concern.[14] Coronary artery disease (CAD) is also one of the most fatal cardiovascular diseases in both developed and developing countries.[15] Being overweight and obesity are among the well-known risk factors of both AF and CAD.[16,17] Patients with CAD are predisposed to AF through atrial ischemia, which leads to disruption of natural expansion and contraction of cardiomyocytes and thus plays an important role in the pathogenesis of AF.[14,18] Endothelial dysfunction is

one of the underlying mechanisms of both AF and CAD.[19]

Today, there are growing numbers of studies evaluating the role of adipose-derived peptides including apelin in the pathogenesis and metabolic dysfunction of different disorders. CAD[20] and AF[21,22] might change apelin serum levels. However, there are still many questions about the role of this adipokine in heart diseases, and some studies have been reporting conflicting results. Furthermore, there is no study comparing apelin levels and its metabolic functions in different cardiovascular diseases. In this preliminary study, serum levels of apelin in overweight or obese patients with AF and CAD, as well as the relationship of apelin with anthropometric measurements and metabolic profile were evaluated.

METHODS

Patients

This study was performed according to the Declaration of Helsinki guidelines. Written informed consent was obtained from all the participants. The study was approved by the ethics committee of Tehran University of Medical Sciences. In this study, 39 patients with documented CAD by angiography and 41 patients with persistent AF and no documented CAD were enrolled. Inclusion criteria were age $>$ 50 years and body mass index (BMI) $>$ 25 kg/m^2. Patients with the previous history of thyroid disorder, valvular heart diseases, heart failure, heart valve replacement surgery and coronary artery bypass surgery in the past 3 months were not included. In addition, patients receiving hormone replacement therapy and patients with current alcohol or drugs consumption were not invited. The following anthropometric measurements were included: standing height without shoes and weight with minimal clothing and without shoes early in the morning. BMI was calculated based on the following formula: weight (kg)/(height [m]^2). Waist circumference was measured at the midpoint between the lower costal margin of the last palpable rib and the top of iliac crests using a tape with an accuracy of 0.5 cm.

Blood Samples

After 12 hours of fasting, 10 mL blood samples were taken between 8 and 10 am from all patients. Samples were centrifuged at 3,000 rpm for 15 minutes and were stored at -80°C. Fasting plasma glucose (FPG) was measured by enzymatic colorimetric method using glucose oxidase standard kit (Pars Azmoon Inc., Tehran, Iran). Insulin levels were quantified by ELISA (Diametra, Italy). Homeostatic model assessment (HOMA-IR) was calculated based on the following formula: HOMA-IR = fasting glucose (mg/dL) $\times$ fasting insulin (μU/mL)/405. Lipid profile, including triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c), was measured using enzymatic colorimetric methods (Pars Azmoon Inc., Tehran, Iran). Moreover, very-low-density lipoprotein (VLDL) levels were calculated using the following formula: VLDL (mg/dL) = TG (mg/dL)/5. Serum levels of apelin were measured using human ELISA kit (Cusabio Biotech Co., Wuhan, China) according to the manufacturer protocol.

Statistical Analysis

To present data, we used mean, standard deviation, median and interquartile range. To examine the normal distribution of data, we used Q-Q plot and Kolmogorov-Smirnov test. Based on this test and the characteristics of the variables, we used *t* test, Mann-Whitney test and Chi-square test (or Fisher exact test, whenever appropriate). To present the differences between 2 groups, we used 95% confidence interval. The correlation between apelin and other variables was assessed by Spearman correlation test. The analysis of covariance was used to consider the effects of probable confounders. Moreover, Partial correlation was used to compute the correlation of different parameters with Apelin, adjusted for the diabetes status. All statistical analysis performed by SPSS (version 22.0, IBM Co., Chicago, IL). $P < 0.05$ was considered statistically significant.

RESULTS

In the present study, 41 patients with persistent AF (70 $\pm$ 7.8 years) and 39 patients with CAD (66 $\pm$ 8.1 years) were studied. The anthropometric measurements and medical history of patients are shown in Table 1, which indicate no significant differences in age, sex, BMI and medical history between the 2 groups.

In the current study, apelin serum levels were not significantly different between 2 groups ($P = 0.433$), even after adjustment for age, sex, diabetes status and HOMA-IR ($P = 0.122$) (Table 2). Differences remained nonsignificant when apelin levels were compared between groups based on sex or BMI subgroups (25 $<$ BMI $<$ 30 kg/m^2, 30 $\leq$ BMI $<$ 35 kg/m^2 and 35 $\leq$ BMI kg/m^2).

The serum levels of FPG and TC were not significantly different between 2 groups ($P = 0.107$ and $P = 0.179$, respectively); whereas fasting insulin, HOMA-IR and LDL-c levels were higher and HDL-c levels were lower in CAD compared with AF group. TG and VLDL levels were significantly higher in patients with CAD; however, this association did not remain after adjustment for diabetes and other confounders (Table 2).

A negative correlation was observed between serum levels of apelin with weight and BMI in all the patients ($r = -0.259$, $P = 0.02$ and $r = -0.25$, $P = 0.026$, respectively). After Partial correlation adjusting the diabetes status, these correlations remained significant ($r = -0.257$, $P = 0.023$ and $r = -0.258$, $P = 0.023$, respectively). Apelin was also inversely correlated with serum levels of FPG ($r = -0.23$, $P = 0.04$), insulin