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Original Article

Clinical implications of serum adiponectin on progression of atrial fibrillation

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ABSTRACT

Background: The association between circulating adiponectin levels and atrial fibrillation (AF) is uncertain. We, therefore, investigated whether an increased serum adiponectin level is implicated in the long-term recurrence of AF after ablation therapy.

Methods: Our study included 100 consecutive patients (88 men; median age, 57.9 ± 10.9 years) who underwent catheter ablation for AF at our hospital between 2011 and 2013. The adiponectin and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured before ablation and compared between those in whom AF recurred and those in whom AF did not recur.

Results: Elevation in adiponectin levels was significantly associated with female sex, non-paroxysmal AF, heart failure, higher NT-proBNP and matrix metallo-proteinase-2 levels, and lower body mass index. After a stepwise adjustment for any potential confounding variables, the adiponectin levels remained significantly associated with female sex (beta=0.2601, P=0.0041), non-paroxysmal AF (beta=0.2708, P=0.0080), and higher NT-proBNP levels (beta=0.2536, P= 0.0138). During the median follow-up period of 26.2 months, AF recurred in 48 of the 100 patients. Stepwise multivariate adjustment showed that an increased log-transformed NT-proBNP (Hazard ratio [HR], 2.18; 95% confidence interval [CI] 1.25–4.00; P=0.0055), longer duration of AF (HR, 1.87; 95%CI 1.01–3.76; P=0.0465), and decreased left ventricular ejection fraction (HR, 0.96; 95%CI 0.93–0.99; P=0.0391) were independent predictors of recurrent AF after catheter ablation, but adiponectin was not.

Conclusions: Our data indicated that adiponectin was partially responsible for progression of AF, but the correlation between adiponectin levels and AF recurrence was not significant.

1. Introduction

Adiponectin is a peptide hormone with insulin-sensitizing, anti-inflammatory, and anti-atherosclerotic effects. Generally, low levels of circulating adiponectin are considered detrimental to the cardiovascular metabolism, contributing to the development of atherosclerosis. However, some studies have shown a link between relatively high levels of plasma adiponectin and heart failure, coronary heart disease, and even mortality [1,2]. In addition, Macheret et al. have shown a significant association between elevated adiponectin levels and increased incidence of atrial fibrillation (AF) among older adults [3].

Over the past decade, catheter-based pulmonary vein isolation (PVI) has become widely accepted as a therapeutic option for AF. However, recurrence of AF after ablation occurs in approximately 20–30% of patients with paroxysmal AF; this proportion is even higher in patients with non-paroxysmal AF. The major contributors to AF recurrence are PV reconnections [4,5] and progressive atrial remodeling, accompanied by an increase in atrial interstitial fibrosis, hypertrophy, or left atrial dilation [6–8]. We previously described the importance of the biomarkers of inflammation and the extracellular matrix turnover as predictors of both progressive atrial remodeling and recurrence of AF after catheter ablation [7,8]. Relatively high plasma adiponectin levels are associated with persistent AF, which is accompanied by an increased serum carboxy-terminal telopeptide level [9] as one of the collagen turnover-related biomarkers. In light of these findings, we hypothesized that circulating adiponectin levels could reflect the atrial remodeling related to the recurrence of AF after ablation. We, therefore, assessed the effect of adiponectin on atrial remodeling and also whether a high adiponectin level was associated with the recurrence of AF after ablation.

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2. Material and methods

2.1. Study patients

One hundred consecutive patients (88 men, 12 women; median age, 57.9 ± 10.9 years; median duration of AF, 48.0 months) who underwent catheter ablation for drug-refractory AF between July 2011 and March 2013 were enrolled in our study. All patients were treated at our hospital, and no patients referred for repeat ablation were included in the study. The group comprised 55 patients with paroxysmal AF (spontaneous termination of AF within 7 days) and 45 patients with non-paroxysmal AF (AF lasting over 8 days). The study protocol was approved by the institutional review board of Nihon University Itabashi Hospital (Date of IRB approval; February 20, 2012; Approval number, RK-120210-4). All patients provided written informed consent for the electrophysiologic study, ablation procedure, and use of their anonymized data in this study. Adequate oral anticoagulation was administered for at least one month prior to the ablation, and all antiarrhythmic drugs were stopped for at least 5 half-lives prior to the ablation. Before the ablation procedure, transesophageal and transthoracic echocardiograms were obtained for each patient, and the standard echocardiographic measurements, i.e., left atrial dimension (LAD) at end systole in the parasternal long-axis view and left ventricular ejection fraction (LVEF) by the Teichholz method, were calculated. In addition, all patients underwent 3-dimensional computed tomography (CT) (320-row detector, dynamic volume CT scanner; Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan) for visualization of the left atrium (LA) and pulmonary veins (PVs). After ablation, all patients were followed up regularly at 1 month, 3 months, 6 months and, subsequently, every 6 months at the outpatient clinic. Routine electrocardiograms (ECGs) were obtained at each visit, and 24-hour Holter monitoring was scheduled to follow the 3-, 6- and 12- month follow-up visits. A blanking period of 2 months was established, and recurrence of AF was defined as any ECG recording of AF or any Holter recording of AF lasting more than 30 seconds.

2.2. Ablation procedure

Ablation was performed under sedation, which was achieved with an intravenous infusion of dexmedetomidine and fentanyl [7,8]. In brief, after vascular access was obtained, a single trans-septal puncture was performed; this was followed by an extensive ipsilateral PVI, guided by 2 Lasso catheters and a 3-dimensional geometric map generated using a NavX (St. Jude Medical, St. Paul, MN, USA) or CARTO (Biosense Webster, Inc., Diamond Bar, CA, USA) mapping system. A 3.5-mm irrigated-tip catheter (NAVISTAR THERMOCOOL; Biosense Webster) or 4-mm irrigated-tip catheter (Safire BLU Duo; St. Jude Medical, Minneapolis, MN, USA) was used for ablation. Radiofrequency energy was delivered at a maximum power output of 20–30 W, and the upper temperature limit was set at 41 °C, with a saline irrigation rate of 17–30 mL/min (COOLFLOW Pump; Biosense Webster) or 13–20 mL/min (Cool Point Irrigation Pump, St. Jude Medical). The endpoint of the PVI was the demonstration of complete entrance and exit block. In patients in whom AF was not terminated by the PVI or in whom sustained AF was inducible after the PVI, linear ablation at the LA roof, LA floor along the coronary sinus, LA appendage ridge, and LA septum (indicated by LA ablation) were performed. The step-by-step ablation procedure was stopped once AF termination was achieved or once all ablation had been performed in patients in whom the AF did not terminate.

2.3. Blood sampling and measurement of the biomarkers of inflammation and extracellular matrix turnover

In the electrophysiology laboratory, just before the ablation, blood samples were drawn from the jugular vein of each patient via a sheath placed for the coronary sinus catheter. The serum high-sensitivity CRP (hs-CRP) was measured using particle-enhanced immunonephelometry (the BN II System; Siemens Healthcare Diagnostics Inc., Marburg, Germany); the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level was determined using a chemiluminescent enzyme immunoassay (Elecsys proBNP sandwich immunoassay; Roche Diagnostics, Mannheim, Germany); the serum matrix metallo-proteinase-2 (MMP-2) level was measured using a 1-step sandwich enzyme immunoassay (antihuman MMP-2 monoclonal antibody; Daiichi Fine Chemical Co., Ltd., Toyama, Japan); and the plasma adiponectin level was measured using a latex particle-enhanced turbidimetric assay (Human Adiponectin Assay Kit; Mitsubishi Kagaku Iatron Inc., Chiba, Japan).

2.4. Division of patients into groups and the comparative study

In addition to the serum biomarkers of inflammation and the extracellular matrix turnover, the following variables and outcomes were recorded: basic patient clinical characteristics, such as the age and sex, body mass index (BMI), type of AF, concomitant medical conditions, medications used, echocardiographic measurements, follow-up time, and recurrence of AF after ablation. The patients were then divided between those in whom AF recurred after ablation and those in whom it did not, and the study variables were compared between the 2 groups.

2.5. Statistical analysis

Continuous variables are expressed as the mean ± SD or median and interquartile range. The between-group differences in the continuous variables were analyzed using a two-tailed t test or Mann–Whitney *U* test. The between-group differences in categorical variables were analyzed using the chi-square test. The correlation between the adiponectin levels and other clinical variables was analyzed using a simple linear regression analysis and Spearman's rank correlation coefficient. To determine the optimal cutoff value of the adiponectin and NT-proBNP levels for recurrence of AF, receiver-operating characteristic (ROC) curves were generated and the area under the curve (AUC) was calculated. The differences between the two AUCs were compared using the z test. In the multiple regression analysis or Cox hazard model, a log transformation was performed for the NT-proBNP levels and AF duration, which were skewed. All variables with a p-value ≤ 0.1 were included in a multiple regression analysis and multivariate Cox proportional hazard model, which was constructed using a stepwise backward elimination method. A Cox proportional hazard model was used to investigate the impact of variables on the recurrence of AF after ablation, and hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained. A p-value < 0.05 was considered significant for all analyses, and all analyses were performed using JMP software version 11.0.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Relation between adiponectin and the covariates of interest

Adiponectin levels were significantly higher in female patients than in male patients (15.0 ± 5.7 vs. 8.7 ± 4.1 μg/mL, $P < 0.0001$), in patients with non-paroxysmal AF than in those with paroxysmal AF (11.7 ± 5.6 vs. 7.7 ± 2.9 μg/mL, $P < 0.0001$), and in patients with heart failure than in those without heart failure (11.9 ± 5.7 vs. 9.0 ± 4.4 μg/mL, $P = 0.0238$). There were no differences in the adiponectin levels between patients with and without hypertension (10.2 ± 4.9 vs. 8.5 ± 4.4 μg/mL, $P = 0.0648$), diabetes mellitus (7.9 ± 5.3 vs. 9.6 ± 4.7 μg/mL, $P = 0.3214$), dyslipidemia (8.0 ± 3.6 vs. 9.9 ± 5.0 μg/mL, $P = 0.0756$), ischemic heart disease (5.2 ± 1.1 vs. 9.7 ± 4.8 μg/mL, $P = 0.0668$), and LA ablation in whom AF was sustained even after the PVI (10.1 ± 5.0 vs. 9.0 ± 4.6 μg/mL, $P = 0.2603$). The correlations between the adiponectin levels and clinical continuous variables, biomarker levels, and echocardiographic variables are shown in Table 1. A weak to moderate correlation was found between the serum adiponectin levels and BMI ($r = -0.2921$, $P = 0.0032$), adiponectin and NT-proBNP ($r = 0.4158$, $P < 0.0001$), and serum adiponectin level and MMP-2 ($r = 0.2025$, $P = 0.0433$). No correlation was found between the serum adiponectin level and any other variables examined. After adjustment by a stepwise multiple regression analysis for the confounding variables, adiponectin remained significantly related to female sex (beta = 0.2601, $P = 0.0041$), non-paroxysmal AF (beta = 0.2708, $P = 0.0080$), non-ischemic heart disease (beta = 0.1980, $P = 0.0189$), and NT-proBNP level (beta = 0.2536, $P = 0.0138$).

3.2. Patient characteristics and ablation outcomes

AF recurred in 48 (48.0%) of the 100 patients during a median follow-up period of 26.2 (range, 4.3 – 45.8) months. The clinical characteristics, medications, biomarker levels, and echocardiographic variables are shown for the total patients and for the patients in each group, in Table 2. AF recurrence was significantly associated with older age, longer duration of AF, non-paroxysmal AF, and the LA diameter ($P < 0.05$ for all). Patients in whom AF recurred had significantly higher adiponectin (10.9 ± 5.5 vs. 8.2 ± 3.6 μg/mL, $P = 0.0045$) and NT-proBNP levels (481 [121–765] vs. 67 [30–255] pg/mL, $P < 0.0001$) (Fig. 1A). When the patients were divided into paroxysmal AF and non-paroxysmal AF groups, no association between adiponectin levels and recurrence of AF was observed in the paroxysmal AF group (8.1 ± 3.1 vs. 7.5 ± 2.8 μg/mL, $P = 0.4801$), and the association was marginal in the non-paroxysmal AF group (12.7 ± 5.9 vs. 9.8 ± 4.8 μg/mL, $P = 0.0999$); however, the association of AF recurrence with the NT-proBNP levels remained significant for both groups (paroxysmal AF: 133 [59–451] vs. 47 [23–98] pg/mL, $P = 0.0138$; non-paroxysmal AF: 635 [356–977] vs. 250 [107–515] pg/mL, $P = 0.0177$). ROC curves for serum adiponectin levels to differentiate recurrence of AF had an AUC of 0.64 (95% CI 0.54– 0.75; $P = 0.0039$), identifying an adiponectin level of ≥ 10.5 μg/mL as the most predictive cutoff value (sensitivity 50.0%, specificity 78.9%) (Fig. 1B). The ROC curves revealed a better prognostic performance for the NT-proBNP (AUC: 0.75, 95% CI 0.65–0.85; $P < 0.0001$) ($P = 0.0075$ vs. AUC for adiponectin levels by z test). The best cutoff value of the NT-pro BNP level was ≥ 132 pg/mL in order to achieve a sensitivity of 75.0% and specificity of 65.4% (Fig. 1B). A stepwise multivariate Cox proportional hazards regression analysis showed that the log-transformed NT-proBNP elevation (HR, 2.18; 95% CI 1.25–4.00; $P = 0.0055$) and the log-transformed

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