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The impact of gender and left atrial blood stasis on adiponectin levels in non-valvular atrial fibrillation ☆

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ABSTRACT

Background: Obesity is a risk factor for non-valvular atrial fibrillation (NVAF), diabetes mellitus, and hypertension. Adiponectin, a unique biomarker of adipose tissue, has antiinflammatory, insulin-sensitizing, and antiatherogenic properties and is known to be higher in women. The relationship between adiponectin, gender, and thromboembolic risk in atrial fibrillation however is unknown.

Methods: The relationship between gender, adiponectin levels, and echocardiographic measures of blood stagnation and left atrial appendage thrombus (LAAT) was assessed in 209 patients with NVAF (55 women and 154 men; mean age 63 ± 14 years) compared to 70 normal sinus rhythm controls (29 women and 41 men; mean age 64 ± 14 years). Total adiponectin was measured by solid-phase ELISA. Demographic and clinical variables of $CHADS_2$ and CHA2DS2-VASc were collected, and spontaneous echocardiographic contrast (SEC), left atrial appendage emptying velocity (LAAEV) and left atrium volume index (LAVI) were measured prospectively.

Results: Elevated adiponectin was associated with advanced cardiovascular pathology and permanent arrhythmia but only in men with NVAF. In NVAF men, a step-wise increase in adiponectin levels was noted relative to increasing intensity of SEC and decreasing LAAEV. Adiponectin level >16657 ng/ml predicted LAAT (OR: 3.66; 95% CI: 1.21–11.48; p = 0.022) after adjustment for CHADS2 score in men but not in women with NVAF.

Conclusions: There is a direct correlation between elevated adiponectin level and the degree of left atrial blood stasis in men but not in women with NVAF. High adiponectin levels can be used as an important variable in the prediction of LAAT.

1. Introduction

Atrial fibrillation and obesity are growing epidemics and are associated with a high morbidity and mortality [1,2]. Obesity is associated with insulin resistance, cardiovascular disease, and risk of developing atrial fibrillation [3]. Adiponectin, secreted by adipose cells, is an adipocytokine that is abundantly circulating in plasma in different isoforms and represents a unique blood marker of adipose tissue [4]. Adiponectin has been shown to have antiinflammatory, insulin-sensitizing effects as well as antiatherogenic properties [5]. Experiments on adiponectin-knockout mice indicate that adiponectin protects against angiotensin II-induced cardiac fibrosis [6]. Several studies have shown that men have lower levels of adiponectin compared to women, likely due to testosterone inhibition of adiponectin production [7,8]. Adiponectin levels are lower in obese individuals, particularly those with visceral adiposity [8,9]. Levels are also lower in patients with type 2 diabetes mellitus, metabolic syndrome, hypertension, and coronary artery disease [10–13].

Despite these associations, the relationship between adiponectin and the thromboembolic complications of atrial fibrillation remains unclear. Adiponectin levels were lower in patients developing postoperative atrial fibrillation compared to those who did not develop this dysrhythmia [14]. The thrombotic complications of post-operative atrial fibrillation are known to be very low. Adiponectin levels were directly related to the duration of atrial fibrillation [15]. Levels were higher in patients with persistent compared to paroxysmal atrial fibrillation or normal sinus rhythm (NSR) [15]. No consistent relationship has been found between adiponectin levels and left atrial size [16,17]. Adiponectin levels did not predict stroke or other cardiovascular complications in 918 stably anticoagulated patients with NVAF [18].

The relationship between gender, adiponectin levels, and echocardiographic measures of blood stagnation and left atrial appendage thrombus (LAAT) was assessed in patients with NVAF compared to normal sinus rhythm controls.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Materials and methods

2.1. Patient recruitment

Study design, patient selection, recruitment, clinical and echocardiographic data collection and assessment have previously been described [19]. Briefly, all patients with NVAF (cases) who had TEE ordered by their primary physician or cardiologist (October 4, 2007–April 27, 2009) were approached for study participation. Patients were excluded from participated if they had: [1] acute illness, stroke, myocardial infarction or surgery within 30 days; [2] more than moderate heart valvular disease; [3] artificial heart valves; [4] prior unprovoked venous or arterial thrombosis; [5] prior major bleeding unrelated to warfarin therapy; [6] liver disease; [7] active malignancy; or [8] hormonal stimulation (estrogen/progesterone therapy or pregnancy). Control subjects in normal sinus rhythm (NSR) with no prior history of atrial fibrillation were recruited from the Primary Care Internal Medicine clinic during their annual medical exam. From our original cohort, a subgroup of subjects was randomly sampled for analysis of this study [19].

2.2. Evaluation with transesophageal echocardiogram

TEE was performed as previously described [20,21]. LAAT was defined as an echogenic mass in the appendage or body of the atrium, distinct from the underlying endocardium and pectinate muscles and detected in more than one imaging plane [20,21]. SEC was defined as a pattern of dynamic "smokelike", slowly swirling, intracavitary echo-densities imaged with gain settings adjusted to eliminate background noise. SEC was graded as "absent", "mild", "moderate", or "severe" according to the published, echocardiographic criteria [22]. LAAEV profiles were measured over 5 consecutive cardiac cycles using pulsed wave Doppler interrogation with the sample volume positioned 1 cm within the orifice of the LAA [23]. The left ventricular ejection fraction (LVEF) was visually estimated. Aortic atherosclerosis severity was defined as "simple" when atheroma thickness was <4 mm and immobile. "Severe atheroma" exceeded 4 mm or contained mobile components [20,21,23]. Given the known difficulties in measuring left atrial volume by TEE, LAVI was assessed by transthoracic echocardiography performed within 1 month of the TEE study and calculated by the biplane area-length method [23]. All echocardiographic images were analyzed by the study cardiologist (NA) who was blinded to clinical and laboratory data. Control subjects in NSR did not have evaluations completed with TEE.

2.3. Study definitions and event adjudication

Congestive heart failure (CHF) was defined as the presence of clinical symptoms and signs of heart failure within the last three months with or without evidence of LV systolic dysfunction by echocardiography [24]. Diabetes mellitus was diagnosed based on the criteria recommended by the American Diabetes Association [25]. Stroke, TIA, and systemic embolization were defined by criteria proposed by the American Heart Association [26]. Body mass index was evaluated as per the World Health Organization weight categories (normal weight: <25 kg/m^2; overweight: 25.0–29.9 kg/m^2; obesity: 30–34.9 kg/m^2; morbidly obese ≥35 kg/m^2) [27]. For cases, the presence of atrial fibrillation was confirmed by either electrocardiogram or Holter monitoring. Atrial fibrillation was classified as "paroxysmal", or "persistent", or "permanent" in accordance with current guidelines [28]. The $CHADS_2$ and CHA2DS2-VASc score was assigned for each case and control [24,29].

2.4. Sample collection

For each subject, 20 ml of citrate blood was collected by antecubital venipuncture using a 19 gauge thin-wall "butterfly" needle with a short plastic tube extension. For NVAF patient (cases) scheduled for electric cardioversion or radiofrequency ablation, phlebotomy was uniformly collected prior to the procedure.

2.5. Plasma adiponectin

Adiponectin in plasma was quantitatively determined by the Quantikine Human Total Adiponectin Immunoassay (R&D Systems, Inc. 614 McKinley Place NE, Minneapolis, MN 55413, USA). This assay uses a 4.5 hour solid-phase ELISA method designed to measure total (low, middle, and high molecular weight) human adiponectin. Assay sensitivity was 0.891 ng/mL, intra-assay precision ranged CV: 2.5%–4.7% and inter-assay precision CV: 5.9%–7.9%. All assays were performed in duplicates.

2.6. Statistical analysis

Demographic, clinical and echocardiographic characteristics and adiponectin levels were compared between cases and controls. Continuous variables (mean ± standard deviation) were compared between groups using a two-sample t-test. Categorical variables (%) were compared using Pearson's Chi-square test for independence. Ordinal variables (%; median with quartiles) were compared using Wilcoxon rank-sum test. Area under the curve (C-index) for adiponectin levels is presented as a receiver operating characteristic (ROC) curve using logistic regression models. Using the cut-point determined by ROC curve, adiponectin levels were dichotomized according to whether the circulating levels were under or over the calculated threshold. This dichotomy for adiponectin levels was assessed into the logistic models to explore the overall predictive value of adiponectin [OR (95% CI), p-value] upon the development of LAAT. This was also done without the dichotomy for adiponectin levels.

3. Results

3.1. Patient population

Demographic and clinical characteristics, separately by gender, are presented for 209 NVAF patients and for 70 NSR controls (Table 1). More NVAF patients had hypertension [132 (63%) vs 33 (49%), p = 0.0339] and took warfarin [164 (78%) vs 1 (2%), p < 0.0001] compared to NSR controls. Of the NVAF cases, female patients were older and more likely to be morbidly obese compared to men. The distribution of all other demographic and clinical variables was similar between genders for both cases and controls. For the case–control comparison, there was no significant difference in either the mean $CHADS_2$ or CHA2DS2-VASc scores. For patients with NVAF (cases) however, the mean $CHADS_2$ (p = 0.0531) and CHA_2DS_2-VASc scores (<0.001) were higher in women compared to men reflecting older age of women and, for the latter tool, the scoring methodology that gives one point for female gender. Detailed information of demographic and clinical characteristics for cases and controls can be found in the Supplement.

Within NVAF cases, 79% had non-permanent atrial fibrillation and 62% had this arrhythmia for more than one year. Markedly enlarged left atrium (LAVI ≥60 mL/m^2) was observed in 19% and severely

Table 1
Demographic and clinical characteristics of non-valvular atrial fibrillation (NVAF) patients (cases) and normal sinus rhythm (NSR) controls.

Variable	NVAF patients			NSR controls		
	Female (N = 55)	Male (N = 154)	P	Female (N = 29)	Male (N = 41)	P
Age, years (mean ± SD)	68.1 ± 11.1	60.9 ± 14.0	0.0007	65.4 ± 14.2	63.4 ± 14.3	0.4922
65–74 years, n (%)	17 (31%)	41 (27%)	0.0274	9 (32%)	8 (20%)	0.4530
≥75, n (%)	16 (29%)	23 (15%)	0.0207	8 (29%)	11 (28%)	0.9229
Female, n (%)						
Body mass Index (mean ± SD)	30.6 ± 8.6	30.4 ± 5.6	0.8264	30.0 ± 7.5	30.1 ± 6.3	0.9593
Body mass index categories			0.0160			0.4087
<25 kg/m^2	15 (27%)	23 (15%)		10 (35%)	10 (24%)	
25.0–29.9 kg/m^2	17 (32%)	57 (37%)		5 (17%)	14 (34%)	
30.0–34.9 kg/m^2	6 (11%)	42 (28%)		6 (21%)	9 (21%)	
≥35 kg/m^2	17 (32%)	32 (21%)		8 (28%)	8 (20%)	
Congestive heart failure, n (%)	17 (32%)	43 (28%)	0.6742	4 (14%)	8 (20%)	0.5391
Hypertension, n (%)	38 (69%)	94 (61%)	0.2879	16 (57%)	17 (43%)	0.2337
Diabetes mellitus, n (%)	8 (15%)	22 (14%)	0.9624	6 (21%)	10 (25%)	0.7317
Stroke/TIA prior, n (%)	12 (22%)	20 (13%)	0.1185	3 (11%)	2 (5%)	0.3788
Vascular diseases, n (%)	16 (29%)	39 (25%)	0.5861	4 (14%)	8 (20%)	0.5277
$CHADS_2$ mean ± SD	1.87 ± 1.6	1.44 ± 1.3	0.0531	1.38 ± 1.4	1.21 ± 1.4	0.6078
CHA_2DS_2-VASc mean ± SD	3.8 ± 2.1	2.16 ± 1.9	<0.001	2.82 ± 1.8	1.61 ± 1.55	0.0037