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Is Adiponectin Elevation Associated with Left Atrial Remodeling and Impaired Mechanical Functions? (a Speckle Tracking Study)

Objectives	Recent studies demonstrated that elevated adiponectin levels predicted an increased risk of atrial fibrillation (AF) and stroke; however, a causal relationship is yet to be unknown. Reduced left atrium (LA) functions detected by two-dimensional echocardiographic speckle tracking (2D-STE) can predict AF development. We aimed to investigate the relationship between adiponectin level and LA functions in hypertensive and diabetic patients at high risk for incident AF.
Material and methods	The study consisted of 80 hypertensive diabetic patients. All patients underwent echocardiography, and venous blood samples were taken. The relationship between adiponectin levels and LA functions was analyzed.
Results	We divided patients into two groups according to the mean adiponectin level (13.63 ng/ml). In the high adiponectin group, the mean age (p=0.001) and high-density lipoprotein (HDL) cholesterol (p=0.015) were higher, whereas estimated glomerular filtration rate (eGFR) (p=0.036) and hemoglobin (p=0.014) levels were lower. Although LA maximum volume, LA minimum volume, and LA pre-A volume were higher in the group with high adiponectin levels, they did not reach a statistical significance. Peak early diastolic LA strain (S-LAe) (p=0.048) and strain rate (SR-LAe) (p=0.017) were lower in this group. Multivariate logistic regression analysis demonstrated that age (p=0.003) and hemoglobin (p=0.006) were predictors of elevated adiponectin levels. On the contrary, S-LAe, HDL cholesterol, and eGFR lost their statistical significance.
Conclusion	In patients with HT and DM, elevated adiponectin level is associated with impaired LA mechanical functions. Increased age and hemoglobin level are independent predictors of elevated adiponectin levels.

Keywords	Adiponectin; atrial mechanical functions; 2D- speckle tracking echocardiography
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Introduction

Adiponectin is a peptide hormone with insulin-sensitizing, anti-inflammatory, and anti-atherosclerotic effects, and it is presumed to be protective against cardiovascular (CV) diseases [1]. However, elevated adiponectin concentration is associated with adverse CV outcomes, including coronary heart disease, heart failure, and all-cause mortality. Vascular injury caused by atherosclerosis results in elevated adiponectin, which is considered the main link between adiponectin and adverse outcomes [2–4]. Recent studies demonstrated that elevated adiponectin predicted an increased risk of atrial fibrillation (AF) and stroke. However, a causal relationship is yet to be established [5, 6].

Left atrial (LA) remodeling involves several pathologic processes, including atrial fibrosis, electrical remodeling, and loss of atrial myocytes [7]. Recent evidence suggests that LA fibrosis is the leading prerequisite for initiation, progression, and persistence of AF. In clinical practice, remodeling is determined by echocardiographic LA enlargement and dysfunction rather than by detection of LA fibrosis.

Unlike conventional echocardiography, evaluation of the LA with two-dimensional echocardiographic speckle tracking (2D-STE) may evaluate reduced LA functions in the subclinical stage [8]. Additionally, reduced LA functions detected by 2D-STE can predict AF development [9].

Hypertension (HT) and diabetes mellitus (DM) are primary triggers causing LA remodeling and subsequent AF. Obesity and a sedentary lifestyle contribute to the incidence and coexistence of these two diseases [10]. In the present study, we hypothesized that adiponectin had contributed to LA remodeling. Hence, we aimed to investigate the relationship between adiponectin concentration and other conventional LA functional variables with LA speckle tracking in hypertensive and diabetic patients who are considered at high risk for incident AF.

Material and methods

Study population

The study was a single-center, cross-sectional research that initially included 100 consecutive patients who received anti-diabetic and anti-hypertensive medical treatment for at least one year. Exclusion criteria were coronary heart disease, left ventricular ejection fraction <50%, chronic renal failure, AF/atrial flutter, history of cerebrovascular disease, second or third-degree atrioventricular block, thyroid dysfunction, and moderate to severe valvular heart disease. Twenty patients with poor echocardiographic windows were excluded, and we analyzed the remaining 80 patients.

Hyperlipidemia was defined as statin use or low-density lipoprotein (LDL) >70 mg/dl. Body-mass index (BMI) was calculated by the formula: weight (kg)/height (m^2). Patients gave informed consent, and the local ethics board approved the study.

Laboratory measurements

Blood samples for determination of adiponectin were collected in EDTA tubes and centrifuged, and the isolated plasma was stored at -80°C until analysis. Plasma adiponectin was measured by a sandwich ELISA assay using commercially available antibodies (Biovendor, Czech Republic).

Peripheral venous blood samples were drawn after overnight fasting and analyzed using vacuum tubes containing EDTA for storage. Hemoglobin, hemoglobin A1c, C-reactive protein (CRP), fasting glucose, total and high-density lipoprotein (HDL) cholesterol concentrations were measured. Concentrations of low-density lipoprotein were calculated using the Friedewald equation. The estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) Study equation [11].

Conventional Echocardiography

The echocardiographic studies were performed using an echocardiography device (VIVID S-5 General Electric Medical System Vingmed Ultrasound AS, Horten, Norway, with software for speckle-tracking of the LV) equipped with a 3.6-MHz transducer. Measurements were obtained by a cardiologist, blinded to results of adiponectin values, according to the American Society of Echocardiography guidelines [12].

LA volume was calculated by the apical four-chamber (A1) and apical two-chamber (A2) measurements using the area-length (L) method (0.85 (A1×A2)). The volume measurements were grouped as 1) LA maximum volume (at ventricular end-systole, just before mitral valve opens), 2) LA minimum volume (at ventricular end-diastole, when the mitral valve closed), and 3) LA pre-A volume (immediately before atrial systole, prior to the electrocardiographic P wave).

Formulas:

1) LA Emptying Volume = (LA maximum volume – LA minimum volume);
2) LA Emptying Fraction (%) = (LA maximum volume – LA minimum volume)/LA maximum volume;
3) LA Active EF (%) = [(LA pre-A volume – LA minimum volume)/LA pre-A volume];
4) LA Passive EF (%) = [(LA maximum volume – LA pre-A volume)/LA maximum volume];
5) LA Expansion index = [(LA maximum volume – LA minimum volume)/LA minimum volume].

Two-dimensional Speckle Tracking Analysis

For analyzing the LA strain, two-dimensional gray-scale images of the LA were acquired in two- and four-chamber views at end-expiratory apnea during five cardiac cycles. Using 2D strain software (EchoPAC108.1.12, General Electric Medical Systems, Horten, Norway), the LA endocardial surface was manually traced using a point and click approach, which permitted automatic definition of an interested region. The software divided the region into six segments and scored the tracking quality for each segment as acceptable or non-acceptable. The non-acceptable segments were excluded from the analysis. Then, global LA strain and strain rate variables were assessed as the average of six segments. The values of LA function variables including peak early diastolic LA strain and strain rate (S-LAe and SR-LAe), peak LA strain and strain rate during ventricular systole (S-LAs and SR-LAs), and peak LA strain and strain rate during atrial systole (S-LAa and SR-LAa) were obtained from mean values of the apical two- and four-chamber views (Figure 1).

Reproducibility

For calculation of intra-observer variability of the LA strain measurements, the evaluation was repeated in 20 randomly selected patients after one month by the same investigator. For calculation of inter-observer variability,

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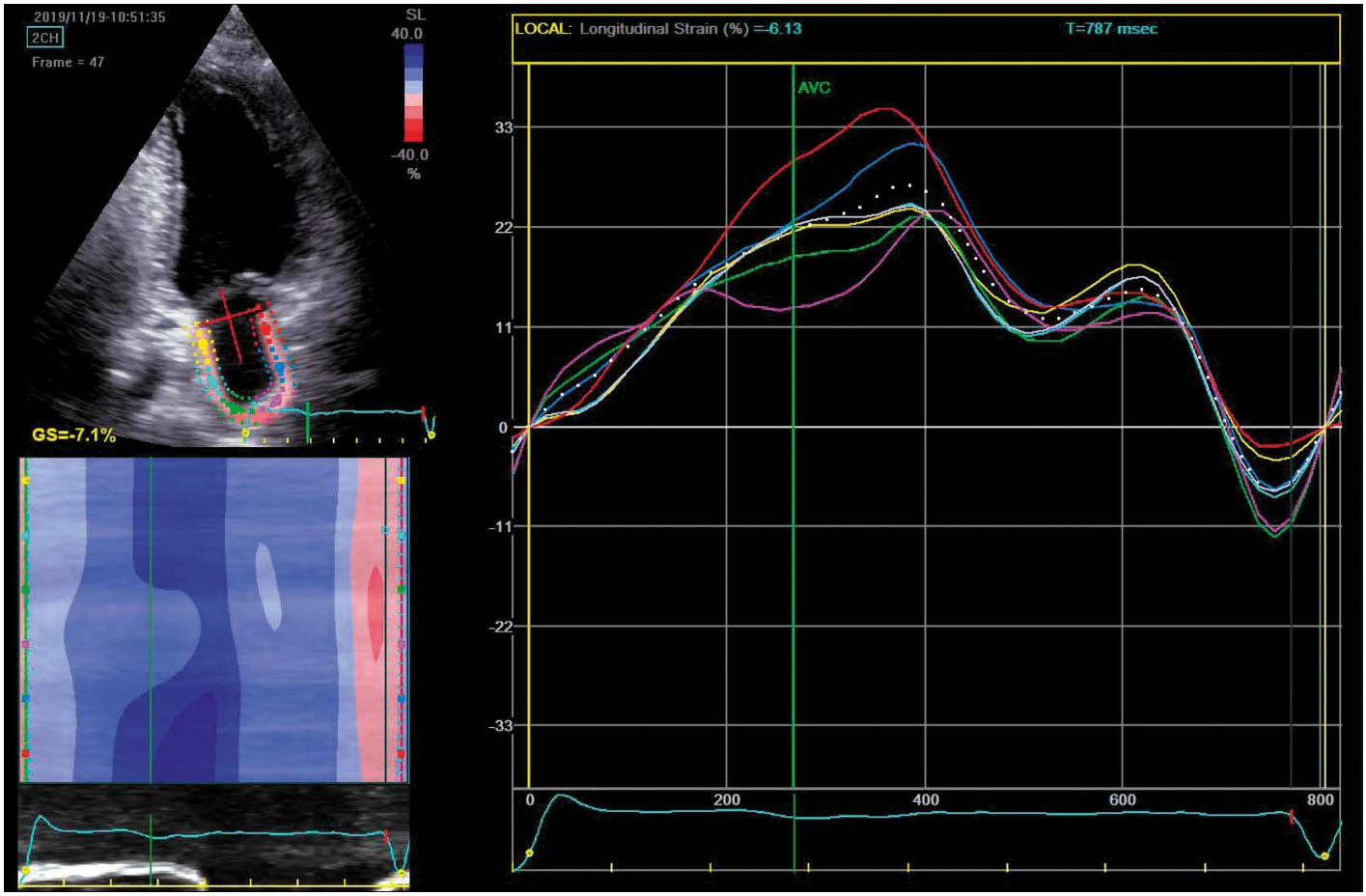
Figure 1. Two-dimensional speckle tracking imaging in the apical two-chamber view



the evaluation was repeated in the same 20 patients by a different investigator, unaware of the initial study results. Intra- and inter-observer variabilities were calculated as the absolute difference between the corresponding two measurements expressed as their mean percentage. The intra-observer coefficient of variation for measurements of S-LAs, S-LAe, and S-LAa were 2.3%, 2.2%, and 1.9%, respectively. The interobserver coefficient of variation for measurement of S-LAs, S-LAe, and S-LAa were 2.7%, 2.1%, and 3.1%, respectively.

Statistical Analysis

Continuous variables are presented as mean values ± standard deviation (SD) or as medians with ranges. Categorical variables are expressed as percentages. Normally distributed, continuous variables were compared with a two-tailed Student t-test or with an ANOVA. Non-normally distributed variables were compared with a Mann-Whitney U test or with a Kruskal-Wallis test. A chi-square test was used to analyze categorical variables. The effects of various variables on OPG were calculated by univariate logistic regression analysis. Logistic regression analyses were used for multivariate analysis of independent variables that were included if they were significantly different in the univariate analyses. Inter-observer agreement of echocardiographic variables obtained from 2D-STE data was calculated using Bland-Altman analysis, and the intra-class correlation coefficient was used to assess intra-observer agreement. All the statistical tests were two-tailed, and a $p<0.05$ value was considered significant. All the analyses were carried out using SPSS version 15 (SPSS, Inc., Chicago, Illinois, US).

Results

The study included 80 consecutive patients (46 female) with a mean age of 58.3 years. According to the adiponectin's mean value (13.63 ng/ml), the patients were divided into two groups. The laboratory and demographic data of the groups were compared with univariate analysis. In the group with high adiponectin, the mean age ($p=0.001$) and high-density lipoprotein (HDL) cholesterol ($p=0.015$) were higher, whereas eGFR ($p=0.036$) and hemoglobin ($p=0.014$) were lower (Table 1). Although it did not reach statistical significance, office systolic and diastolic blood pressure, hemoglobin A1c, and fasting glucose tended to be higher in this group.

Echocardiographic values are shown in Table 1. In conventional echocardiography, there was no difference between LA emptying volume, LA emptying fraction, LA active-passive ejection fraction (EF), and LA expansion index

Table 1. Clinical demographic, laboratory, and echocardiographic characteristics of the groups

Variable	Group 1: Adiponectin<Mean, n=54	Group 2: Adiponectin>Mean, n=26	p
Demographic and laboratory characteristics			
Age (years)	55.7±8.8	62±5.7	0.001
Male, (n, %)	25 (46.3%)	9 (34.6%)	0.328
Hyperlipidemia (n, %)	51 (94.4%)	22 (84.6%)	0.150
Current smoker (n, %)	8 (14.8%)	4 (15.6%)	0.140
BMI (kg/m^2)	32.9±4.3	32.6±5.1	0.641
Office- Systolic BP (mmHg)	153 (138.7–160.2)	154 (142.7–160.7)	0.275
Office- Diastolic BP (mmHg)	89.6±11.1	91.2±10.1	0.523
HT-duration time (year)	6 (2.0–10.0)	5 (2.0–6.5)	0.328
DM-duration time (year)	5.5 (1.7–10.0)	5.5 (3.7–10)	0.323
Fasting plasma glucose (mg/dl)	125 (116–178.2)	139 (114-166)	0.988
Total cholesterol (mg/dl)	193.1±42	198.8±42.8	0.574
LDL- cholesterol (mg/dl)	130.6±33.2	127.03±32.1	0.664
HDL- cholesterol (mg/dl)	43.2±8.1	48.5±10.3	0.015
HbA1c (%)	7.6 (6.8–8.5)	7.9 (7.2–8.8)	0.319
CRP (mg/l)	0.19 (0.09–0.41)	0.28 (0.11–0.42)	0.438
Se Creatinine (mg/dl)	0.78±0.18	0.80±0.14	0.594
MDRD eGFR (mL/min/1.73 m^2)	90.1±18.2	80.7±13.4	0.036
Hemoglobin (mg/dl)	13.5±1.2	12.8±1.04	0.014
Calcium-channel-blocker (n, %)	18 (32.1%)	8 (33.3%)	0.557
Beta-blocker (n, %)	21 (38.9%)	9 (30.6%)	0.454
ACE inhibitor, ARB (n, %)	48 (88.9%)	21 (80.8%)	0.256
Diuretic (n, %)	24 (44.4%)	10 (38.5%)	0.397
Statin (n, %)	23 (42.6%)	18 (42.3%)	0.587
OAD (n, %)	54 (100)	26 (100)	–
Insulin (n, %)	7 (13.0)	3 (11.5)	0.584
Echocardiographic Variables			
LA MinVol (ml)	23.73 (18.6–30.7)	27.35 (18.7–35.5)	0.116
LA MaxVol (ml)	50.4 (40.8–62.3)	52.9 (41.4–66.7)	0.302
LA Pre A Vol (ml)	34.6 (30.3–47.8)	39.1 (29.5–52.3)	0.187
LA EmptyVol (ml)	27.2±8.8	26.5±8.9	0.740
LA Empty Frak %	52.7±10.4	48.9±10.1	0.129
LA Pasif EF %	25.9±11.2	27.6±8.5	0.530
LA Aktif EF %	37.04±10.4	33.9±11.6	0.234
LA ExpInd	1.05 (0.89–1.4)	1.06 (0.78–1.34)	0.213
S-LAs (%)	36.3±9.2	32.7±7.8	0.091
S-LAe (%)	18.02±6.2	15.2±4.5	0.048
S-LAa (%)	16.8 (15.3–21.9)	17.8 (12.8–20.8)	0.549
SR-LAs (s-1)	1.52±0.43	1.36±0.31	0.077
SR-LAe (s-1)	1.50±0.56	1.23±0.31	0.017
SR-LAa (s-1)	2.43±0.58	2.23±0.65	0.169

Data are mean ± SD or median and (range, [25% percentile-75% percentile]). BMI, body mass index; BP, blood pressure; HT, hypertension; DM, diabetes mellitus; LDL, low-density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein; MDRD, modification of diet in renal disease; eGFR, estimated glomerular filtration fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; OAD, oral anti-diabetic; LA, left atrium; S-LAs, peak left atrial strain during ventricular systole; S-LAe, peak left atrial strain at early diastole; S-LAa, peak left atrial strain at atrial systole; SR-LAs, peak left atrial strain rate during ventricular systole; SR-LAe, peak left atrial strain rate at early diastole; SR-LAa, peak left atrial strain rate at atrial systole.

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Table 2. Logistic regression analysis of the relationship between variables and adiponectin

Variable	Univariate analysis			Multivariate analysis		
	OR	95 CI%	p	OR	95 CI%	p
Age	1.108	1.036 – 1.185	0.003	1.149	1.047 – 1.260	0.003
eGFR	0.965	0.933 – 0.999	0.041	–	–	–
HDL	1.067	1.010 – 1.126	0.020	1.070	0.990 - 1.156	0.088
Hgb	0.563	0.350 – 0.906	0.018	0.394	0.178 – 0.874	0.006
GLSe LA	0.911	0.829 – 1.002	0.054	–	–	–
GLSRe LA	0.171	0.041 – 0.703	0.014	–	–	–

MDRD, Modification of Diet in Renal Disease; eGFR, Estimated glomerular filtration fraction; S-LAe, peak left atrial strain at early diastole; SR-LAe, peak left atrial strain rate at early diastole.

measurements that reflected LA systolic, diastolic and booster pump functions. Although the values of LA maximum volume, LA minimum volume, and LA pre-A volume were higher in the group with high adiponectin, they did not reach statistical significance. In LA strain and strain rate analyses, S-LAe (%) (p=0.048) and SR-LAe (s-1) (p=0.017) were lower in the group with high adiponectin. S-LAs (%) tended to be was lower in this group but not statistically significant (p=0.091). There were no differences in other variable between the groups (Table 1).

Parameters found to be significant in the univariate analysis were then included in a backward multivariate logistic regression analysis. The results showed that age (OR 1.149, 95% CI 1.047–1.260, p=0.003) and hemoglobin (OR 0.394, 95% CI 0.178–0.874, p=0.006) were predictors of elevated adiponectin. Conversely, S-LAe, HDL cholesterol, and eGFR lost statistical significance (Table 2).

Discussion

In the current study, we found a decrease in LA functions as analyzed by LA strain/strain rate in hypertensive and diabetic patients with high adiponectin. However, this relationship was not independent of other factors. We determined that age and hemoglobin were predictors of elevated adiponectin. Our study is the first to investigate adiponectin and LA mechanical functions using strain and strain rate analysis.

The present study showed that the association between adiponectin and AF might not be directly related to impaired LA mechanical functions; therefore, this relationship seems to be based on other mechanisms rather than LA fibrosis or myocyte loss. Macheret et al. found that adiponectin elevation was associated with incident AF independent of LA measurements and NT-pro BNP concentration [13]. Another study, included patients who underwent catheter ablation for AF, found similar results [14]. These studies showed that adiponectin elevation was associated with AF recurrence independent of LA volume and LVEF [1, 14].

Although adiponectin is generally synthesized in adipocytes, it can also be synthesized in many other cell types such as bone, skeletal muscle, liver, and myocardium [15]. Local adiponectin synthesized in cardiomyocytes promotes glucose and fatty acid uptake and phosphorylation of 5 'adenosine monophosphate-activated protein kinase [16]. Ybarra et al. showed a paradoxical inverse relationship between LA volume and adiponectin in their study, including findings in obese patients [17]. These observations suggested that adiponectin might not cause atrial fibrosis directly but rather contributed to the interplay of other accompanying conditions responsible for the development of atrial fibrosis.

A disconnect between adiponectin and its receptor might be one of the underlying mechanisms responsible for our findings [18]. Prior studies demonstrated that adiponectin supplementation reduced the risk of myocardial fibrosis [19]. This supports adiponectin's anti-fibrotic role. Adiponectin also eliminates apoptotic cells and reduces inflammation. Thus, elevated adiponectin, which is considered to by anti-inflammatory and anti-fibrotic in patients with AF, may be caused by disconnection between adiponectin and its receptor [19]. Increased gene expression of adiponectin secondary to receptor disconnection in the context of chronic inflammation may be the reason for elevated adiponectin [14]. Interestingly, we found that the LA strain rate was reduced in patients with elevated adiponectin, but other factors confounded this. This finding supported our adiponectin-receptor disconnection hypothesis.

Despite its beneficial effects, high adiponectin was associated with mortality and AF development in patients with CV diseases and heart failure [5]. The researchers hypothesized that this might be secondary to the dysfunction between adiponectin and its receptor [5]. It is assumed that chronic inflammation results in increased adiponectin production, and as the process persisted, adiponectin is unable to bind to its receptor and/or produces an insufficient post-receptor binding response within cells. Even if patients

with elevated adiponectin had poorer LA mechanical function, this relationship was not independent of other factors supporting our hypothesis. Insufficient adiponectin in LA remodeling may cause LA fibrosis. Therefore, AF may develop in patients with high adiponectin. Further research at the molecular and cellular levels may clarify questions about this issue and perhaps pave the way for a new therapy for treatment of AF.

Limitations

The sample size of subjects was relatively small to generalize our findings. Because dedicated software for LA strain had not yet been released, we used the current software for analysis of the LV to study LA strain.

Conclusion

In patients with HT and DM, elevated adiponectin was associated with impaired LA mechanical function. Increased age and hemoglobin level were independent predictors of elevated adiponectin.

No conflict of interest is reported.

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