Elevated Plasma Adiponectin Levels Are Associated with Abnormal Corrected QT Interval in Patients with Stable Angina

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Summary

Low-circulating levels of adiponectin (ADPN) are associated with obesity, diabetes mellitus, and coronary artery disease. On the contrary, some studies have demonstrated a link between relatively high levels of plasma ADPN and heart failure, atrial fibrillation, and adverse outcome. However, little is known about the relationship between ADPN level and prolonged QT interval. The aim of this study was to investigate the association between plasma ADPN levels and prolonged QT interval in patients with stable angina.

In this retrospective study, because the diverse disease severity and condition of the study population may have affected the results, we chose individuals with stable angina. Plasma ADPN concentrations were measured using enzyme-linked immunosorbent assays. A 12-lead ECG recording was obtained from each patient.

We enrolled 479 stable-angina patients. Patients with an abnormal corrected QT (QTc) interval had higher median plasma ADPN levels than those with normal QTc intervals. Age- and sex-adjusted ADPN levels were positively associated with heart rate, QTc interval, left ventricular mass index, and creatinine but negatively associated with left ventricular ejection fraction, waist circumference, current smoking, total cholesterol, triglycerides, low-density lipoprotein cholesterol, albumin, and estimated glomerular filtration rate. A multiple logistic regression analysis revealed ADPN as an independent association factor for abnormal QTc interval. Increasing concentrations of sex-specific ADPN were independently and significantly associated with abnormal QTc interval, even after full adjustment of known biomarkers.

Our results indicate that ADPN may play a role in the pathogenesis of abnormal QTc interval in patients with stable angina.

(Int Heart J 2020; 61: 29-38)

Key words: Adverse outcome, Left ventricular ejection fraction

Corrected QT (QTc) interval prolongation is one of the most important electrocardiographic abnormalities and an important cause of sudden cardiac death.¹⁾ Over the last decades, research has mainly focused on the genetic pathogenesis of a prolonged QT interval.²⁾ In a population-based sample, Kim, *et al.* reported a positive association between an increased blood level of C-reactive protein (CRP) and heart rate QTc duration.³⁾ Kazumi, *et al.*⁴⁾ also reported a significant association between CRP and QTc in a cohort of young healthy men, and experimental studies have demonstrated that the

TNF-alpha system influences calcium^{5,6)} and potassium^{7,8)} channels that then affect QT time and susceptibility to arrhythmias.⁹⁾ Furthermore, previous studies have demonstrated that interleukin 6 (IL-6) plays a major role in the pathophysiology of cardiac arrhythmias.^{10,11)} Hence, increased levels of inflammatory mediators in patients with stable angina may provoke cardiac fibrosis, vascular damage, sympathetic overactivity, and ion channel malfunction,¹²⁻¹⁵⁾ resulting in a higher risk of cardiac arrhythmias and death.

Adiponectin (ADPN) comprises 244 amino acid pep-

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This research was supported by E-Da Hospital of the Republic of China, Taiwan, under contracts ECAHI105001 and EDCHP107001.

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Received for publication May 28, 2019. Revised and accepted September 4, 2019.

Released in advance online on J-STAGE January 17, 2020.

doi: 10.1536/ihj.19-270

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tides with insulin-sensitizing, anti-inflammatory, and anti-atherosclerotic effects. Low levels of circulating adiponectin are considered to be detrimental to cardiovascular metabolism and to contribute to the development of atherosclerosis. However, some studies have reported associations between high levels of plasma ADPN and coronary heart disease, heart failure (HF), atrial fibrillation (AF), and even mortality.¹⁶⁻¹⁸⁾ Lee, *et al.*¹⁹⁾ demonstrated that the ADPN level and left ventricular mass index were positively associated in subjects at high risk of left ventricular hypertrophy. Of note, ADPN levels have been demonstrated to be increased in patients with chronic inflammatory and autoimmune diseases such as type I diabetes, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and chronic systolic HF. In addition, ADPN levels have also been reportedly increased in patients with hypertrophic cardiomyopathy associated with diastolic dysfunction.²⁰⁾ However, to the best of our knowledge, little is known about the relationship between the ADPN level and cardiac electro-pathology, and if the study population had different diseases (e.g., acute coronary syndrome and myocardial infarction), the diverse disease severity and condition of the study population may have affected the results. As a result, we chose individuals with stable angina in this study. Therefore, the aim of this study was to investigate whether ADPN levels were associated with a prolonged QTc interval in a cohort of patients with stable angina.

Methods

Study population: The study population included 479 consecutive consenting patients who underwent angiography for the first time with a clinical diagnosis of stable angina from January 2007 to December 2017 at the Cardiovascular Clinic of E-Da Hospital. Stable angina pectoris was defined as effort-related chest pain without evidence of recent deterioration or rest pain in the previous 6 months. Patients with an inflammatory disease (including infection or sepsis), collagen disease, liver disease, malignancy, steroid use, a bundle branch block pattern, and a history of psychosis were excluded from the study. In addition, patients taking medications that can influence the QT interval including psychotropic medications, class I (e.g., quinidine, procainamide, mexiletine, and flecainide) and class III (e.g., amiodarone, dronedarone, and vernakalant) anti-arrhythmic medications, and ranolazine medication were also excluded from the study. The study protocol was approved by the Human Research Ethics Committee of E-Da Hospital, and written informed consent was obtained from each patient.

Before the coronary angiography examination, each patient had a detailed interview about his or her medical and personal history. Body height, weight, waist, and hip circumferences were measured, and the body mass index (BMI) was calculated. The waist circumference was measured at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest. The hips were measured at their widest point. Blood pressure was measured in the morning (readings were taken twice, at least 2 minutes apart), on the right upper arm in line with

the heart using a mercury column sphygmomanometer with the participant in a sitting position after a minimum rest period of 5 minutes. Type 2 diabetes (T2DM) was defined as a past or current diagnosis of T2DM and/or the need for medical therapy, according to the World Health Organization criteria.²¹⁾ Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg, a diastolic blood pressure (DBP) ≥ 90 mmHg, or a patient's current antihypertensive treatment. Hyperlipidemia was defined as a triglyceride (TG) level ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) level < 35 mg/dL for men or < 39 mg/dL for women, total cholesterol ≥ 200 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL, or treatment for lipid disorders according to the Adult Treatment Panel III criteria.²²⁾ Smoking was classified as never having smoked, former smoker (ceased smoking for at least 1 year), or current smoker. Former and current smokers were analyzed as one group and compared to those who had never smoked.

Laboratory measurements: Plasma biochemical parameters were measured after patients' fasting for 8 hours and before the coronary angiography examination. All biochemical analyses were carried out within 2 hours of blood sampling at the E-Da Hospital laboratory. Complete blood cell counts and serum creatinine, sodium, potassium, calcium, uric acid, albumin, glucose and lipid profiles (including plasma TGs, total cholesterol, LDL-C, and HDL-C) were determined in all patients using standard commercial methods on a parallel-multichannel analyzer (Hitachi 7170A, Tokyo, Japan). In addition, the concentrations of plasma ADPN were determined using commercial enzyme-linked immunosorbent assay kits (R&D Systems Inc., Minneapolis, MN, USA). The dilution curve was parallel to the standard curve. The intra-assay and inter-assay coefficients of variation of the assay were 2.5% to 4.7% ($n = 3$) and 6.8% to 6.9% ($n = 3$), respectively. Plasma CRP was measured using a high-sensitivity method (IMMAGE; Beckman Coulter, Immunochemistry Systems, Brea, CA, USA) with a detection limit of 0.2 mg/L. The intra-assay coefficient of variation was 4.2%-8.7% for high-sensitivity (hs)-CRP. Samples were measured in duplicates in a single experiment.

The estimated glomerular filtration rates (eGFRs) were calculated using the chronic kidney disease (CKD)-EPI two-concentration race equation,²³⁾ and the status of CKD was confirmed by follow-up eGFR measurements after 3 months. We used the modified National Kidney Foundation classification of CKD.²⁴⁾ An eGFR < 60 mL/minute per 1.73 m^2 was defined as CKD, and patients with stage 1 or 2 CKD (eGFR ≥ 60 mL/minute per 1.73 m^2) were classified as not having CKD.²⁵⁾

Angiographic definitions: Coronary angiograms were obtained from each patient according to standard techniques, and the severity of stenosis was assessed using quantitative coronary angiography (QCA). Angiograms and QCA analyses were performed by at least two experienced interventional cardiologists blinded to the clinical information and serologic parameters and scored according to two scoring systems: (1) The possible scores of this index ranged from 0 to 3 diseased vessels, and the criterion for one-, two-, or three-vessel disease was a $>75\%$ reduction

in the internal diameter. The diameter of stenosis of the left main coronary artery could not exceed 50%. (2) In the modified Gensini scoring system, weights are assigned to each coronary segment depending on vessel size and importance, ranging from 0.5 to 5.0; segments serving larger regions of the myocardium are more heavily weighted. The narrowing of the coronary artery lumen is rated 2 for 0%-25% stenosis, 4 for 26%-50%, 8 for 51%-75%, 16 for 76%-90%, 32 for 91%-99%, and 64 for 100%. The modified Gensini index is the sum of the total weights for each segment.^{26,27)}

Electrocardiogram measurements: The echocardiography tests were performed during the resting period, in the morning and in the left lateral position. All the echocardiographic measurements followed the recommendations of the American Society of Echocardiography, and at least three cycles were analyzed for each variable. The echocardiography machine used in our study is the GE Healthcare, General Electric Company, models Vivid 7 System (USA) with 3-7 mHz transducers and features for obtaining the M-mode, two-dimensional and Doppler (pulsed, continuous, color and tissue) echo modalities. All the long and short parasternal and apical axes 2, 3, 4, and 5 chambers' view examination were performed. The cardiac structure and function were assessed from the M-mode guided by two-dimensional imaging. In addition, left ventricular mass was calculated using a two-dimensional method and indexed to the body surface area. Left ventricular mass indexes (LVMI) of >131 g/m² for men and > 100 g/m² for women were accepted as left ventricular hypertrophy (LVH). The left ventricular ejection fractions (LVEFs) were calculated from the apical four-chamber views using the modified Simpson method and left ventricular systolic dysfunction (LVSD) was defined as LVEF ≤ 50%.

QT and QTc interval measurements: Twelve-lead ECGs were recorded for analysis during the baseline examination using a standardized protocol when the patient was enrolled in the study. At least two cardiologists who were blinded to this study manually measured the QT interval. The QT interval was defined as the interval between the first deflection of the QRS complex and the end of the T wave. The end of the T wave was determined by extending a tangent from the steepest portion of the downslope of the T wave until it crossed the T-P segment. The QT and RR intervals were averaged over three consecutive complexes in lead II in sinus rhythm. During other rhythms, QT and RR intervals were averaged over all complexes on the 10-second lead II rhythm strip on the 12-lead ECGs. The QTc intervals were calculated using Bazett's formula ($QTc = QT / \sqrt{RR}$).^{28,29)} In brief, the ECG tracings were blinded to the participants' demographics and first analyzed by two independent cardiologists and a senior supervising cardiologist. Inter-reader discrepancies were resolved by direct comparison and adjudicated by the supervising cardiologist. If the T wave amplitude was too flat to identify the end of the wave or there was large big differences between the QTc measurements by the two independent cardiologists that failed to be adjusted by the supervisor, the data were excluded from our study. The final QTc value was the average from

the QTc values calculated by the supervisor and the two blinded independent cardiologists. Inter-reader reproducibility assessments for the QT measurement indicated a coefficient of reliability of 0.995 and a Pearson's correlation coefficient of 0.995. Comparing inter-reader QT measurements using the paired *t*-test did not achieve statistical significance (*P* = 0.35). In addition, extremely rapid (> 150 bpm) and extremely slow (< 40 bpm) heart rate recordings were also be excluded to eliminate the influence of heart rate on QT measurements.^{30,31)} In this study, QTc prolongation was categorized into three sex-specific categories based on the opinion of an *ad hoc* group according to the latest European regulatory guidelines and a previous study.³²⁾ The cutoff points were ≤ 450 ms (normal), 451-470 ms (borderline), and > 470 ms (prolonged) in women and ≤ 430 ms (normal), 431-450 ms (borderline), and > 450 ms (prolonged) in men.

Follow-up: Patients were clinically re-evaluated 3, 6, and 12 months after hospital discharge and then annually to record clinical conditions until December 2017. Furthermore, all participants entered a disease management program at the cardiovascular clinic, and each patient received a follow-up questionnaire from our trained nurse during December 2017, re-evaluating the occurrence of major adverse cardiac events (MACE) during the entire follow-up period. If patients did not respond to the questionnaire, personal telephone contact was made with them or their relatives. Further information was obtained by reviewing hospital discharge reports relating to any other re-admission during the follow-up period. The performance of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was validated by reviewing original procedure protocols. Outcome was adjudicated by two independent observers who were blinded with respect to the patients' baseline clinical and laboratory data.

Statistical analysis: Data normality was assessed using the Kolmogorov-Smirnov test. Continuous, normally distributed variables were presented as mean ± standard deviation, and nonnormally distributed variables, as median (interquartile range [IQR]). Statistical differences between variables were compared using one-way analysis of variance for normally distributed variables, followed by Tukey's pairwise comparison. Before performing the statistical tests, serum or plasma levels of TG, creatinine, hs-CRP, ADPN, and the Gensini score were logarithmically transformed to achieve a normal distribution. Categorical variables were reported as frequencies and/or percentages, and inter-group comparisons were performed using the chi-squared test. Risk factors for arrhythmia such as age, sex, BMI, SBP, fasting glucose, total cholesterol, sodium, potassium, calcium, use of beta-blockers, diuretics, and statins; diseases of CKD, LVH, and LVSD; and ADPN were assessed for independent associations with the presence of an abnormal QTc interval in a multiple logistic regression analysis using patients with normal and borderline QTc intervals as the reference category. Pearson's correlation coefficients and multiple linear regression analyses were used to examine the correlations and independence between plasma ADPN and the values of other parameters.

Table I. Baseline Characteristics of the Study Population Stratified by Category of QTc Prolongation at Baseline*

Variables	Normal	Borderline	Abnormal	P-value
Number	202	113	164	
Sex (male/female)	148/54	91/22	131/33	0.206
Age (years)	70.8 ± 11.9	74.1 ± 12.2	76.4 ± 12.5	< 0.0001
Hypertension, <i>n</i> (%)	147 (72.8)	85 (75.2)	124 (75.6)	0.801
Hyperlipidemia, <i>n</i> (%)	153 (75.7)	69 (61.1)	104 (63.4)	0.008
Diabetes mellitus, <i>n</i> (%)	75 (37.1)	47 (41.6)	91 (55.5)	0.002
LVSD, <i>n</i> (%)	24 (11.9)	24 (21.2)	64 (39.0)	< 0.0001
Current smoking, <i>n</i> (%)	82 (40.6)	54 (47.8)	68 (41.5)	0.435
Heart rate (bpm)	69.6 ± 17.8	77.7 ± 18.5	87.5 ± 19.9	< 0.0001
QT interval (ms)	391 ± 45	399 ± 42	412 ± 53	0.0001
Corrected QT interval (ms)	412 ± 32	445 ± 9	488 ± 30	< 0.0001
Body mass index (kg/m ²)	25.5 ± 4.1	25.6 ± 3.3	24.7 ± 4.0	0.081
Waist circumference (cm)	90.6 ± 10.5	92.8 ± 7.7	90.9 ± 10.8	0.252
Systolic blood pressure (mmHg)	133 ± 21	134 ± 24	134 ± 25	0.872
Diastolic blood pressure (mmHg)	77 ± 13	77 ± 11	78 ± 15	0.722
Sodium (mmol/L)	139.0 ± 3.3	139.0 ± 4.8	138.2 ± 5.0	0.148
Potassium (mmol/L)	3.9 ± 0.5	3.9 ± 0.5	3.9 ± 0.8	0.954
Calcium (mmol/L)	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.3	0.387
Fasting glucose (mmol/L)	8.3 ± 4.6	8.2 ± 4.2	9.5 ± 4.9	0.031
HbA1c (%)	6.9 ± 1.8	6.8 ± 1.3	7.4 ± 2.0	0.032
Total-cholesterol (mmol/L)	4.7 ± 1.2	4.4 ± 0.9	4.6 ± 1.3	0.063
Triglycerides (mmol/L)	1.3 (0.9-2.1)	1.4 (1.0-2.0)	1.3 (0.9-1.9)	0.363
HDL-cholesterol (mmol/L)	1.0 ± 0.4	1.0 ± 0.3	1.0 ± 0.3	0.403
LDL-cholesterol (mmol/L)	2.9 ± 1.1	2.6 ± 0.7	2.8 ± 1.0	0.027
Uric acid (umol/L)	386.6 ± 119.0	422.3 ± 172.5	440.2 ± 142.8	0.012
Creatinine (umol/L)	106.1 (97.2-132.6)	114.9 (97.2-150.3)	123.8 (97.2-168.0)	< 0.0001
Albumin (g/L)	38 ± 5	39 ± 4	38 ± 4	0.0001
Estimated GFR (mL/minute/1.73 m ²)	59.9 ± 19.8	52.8 ± 22.7	48.3 ± 23.4	< 0.0001
Hs-CRP (mg/L)	2.6 (1.1-7.5)	4.4 (1.3-13.2)	8.7 (2.2-19.8)	0.006
White blood cell count (× 10 ⁹ /L)	8.325 ± 3.019	8.620 ± 3.420	9.070 ± 3.632	0.105
Adiponectin (μg/mL)	3.4 (1.9-6.0)	4.3 (2.0-9.3)	5.7 (2.8-11.3)	0.009
No. of diseased coronary arteries	2.0 ± 1.0	2.1 ± 0.9	2.0 ± 1.0	0.542
Gensini score	40.0 (18.8-80.0)	52.5 (19.8-84.3)	44.5 (18.0-92.5)	0.586
Percutaneous coronary intervention	190 (94.1)	108 (95.6)	155 (94.5)	0.850
Number of stent	70 (34.7)	34 (30.1)	41 (25.0)	0.135
Beta-blockers, <i>n</i> (%)	120 (59.4)	51 (45.1)	80 (48.8)	0.025
Diuretics, <i>n</i> (%)	42 (20.8)	40 (35.4)	64 (39.0)	0.001
Statins, <i>n</i> (%)	136 (67.3)	61 (54.0)	87 (53.1)	0.011

Data are expressed as mean ± SD, number (%), or median (interquartile range). LVSD indicates left ventricular systolic dysfunction. HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR, glomerular filtration rate; and Hs-CRP, high-sensitivity C-reactive protein. *Classification of QTc prolongation: normal men, ≤ 430 ms; women, ≤ 450 ms; borderline men, 431-450 ms; women, 451-470 ms; abnormal men, ≥ 451 ms; women, ≥ 471 ms.

We also recorded the occurrence of MACEs after the patients had been discharged from the hospital. MACEs were defined as all-cause mortality or re-hospitalization for a cardiovascular-disease-related illness including HF, reinfarction (nonfatal), recurrence of angina pectoris, and repeated PCIs or CABG. Furthermore, we divided the distribution of plasma ADPN levels into tertiles according to sex. Laboratory features, LVEF, LV mass index, and ECG parameters in each tertile were described and tested for trend across plasma ADPN tertiles using a linear regression analysis and the Cochran-Armitage trend test for categorical variables such as MACEs and other diseases. Moreover, a multiple logistic regression analysis was used to assess the OR for the presence of an abnormal QTc interval in subjects in the highest ADPN tertiles compared to those in the lowest tertile. Statistical significance was accepted if $P < 0.05$. All data were analyzed using JMP

version 7.0 for Windows (SAS Institute, Cary, NC, USA).

Results

The patients' baseline clinical, biochemical, and angiographic characteristics are listed in Table I. Two hundred and two patients were categorized as having a normal QTc interval, compared to 113 patients with borderline QTc prolongation and 164 patients with an abnormal QTc interval (Table I). The patients with an abnormal QTc interval had a significantly higher plasma ADPN level than those with a normal QTc interval (5.7 μg/mL [IQR: 2.8-11.3] versus 3.4 μg/mL [IQR: 1.9-6.0], $P = 0.009$). In addition, the patients with an abnormal QTc interval were older and had higher rates of diabetes mellitus, LVSD, and receiving diuretic therapy. Moreover, the patients with an abnormal QTc interval (prolonged QT interval) had

Table II. Multiple Logistic Regression Analysis with the Presence of Abnormal Corrected QT Interval as the Dependent Variable

	OR	95% Confidence Interval	P-value
Age	1.03	0.99-1.06	0.068
Sex	2.85	1.33-6.10	0.007
Body mass index	1.01	0.93-1.10	0.840
Systolic blood pressure	1.01	0.99-1.02	0.371
Fasting glucose	1.00	0.99-1.00	0.860
Total cholesterol	1.00	0.99-1.01	0.539
Sodium	0.96	0.90-1.03	0.235
Potassium	0.83	0.53-1.31	0.427
Calcium	0.83	0.58-1.19	0.320
Use of beta-blockers	0.96	0.52-1.79	0.900
Use of diuretics	1.37	0.70-2.68	0.353
Use of statins	0.74	0.40-1.39	0.354
CKD	1.34	0.67-2.70	0.412
LVH	0.95	0.38-2.34	0.905
LVSD	1.38	0.67-5.99	0.211
Adiponectin	1.05	1.00-1.11	0.048

CKD indicates chronic kidney disease; LVH, left ventricular hypertrophy; and LVSD, left ventricular systolic dysfunction.

higher levels of uric acid, creatinine, and hs-CRP than those with a normal QTc interval. In addition, the patients with an abnormal QTc interval had a higher fasting glucose level and HbA1c than those with a borderline QTc interval and had a higher heart rate than the normal and borderline QTc interval groups. The patients with an abnormal QTc interval also had lower levels of albumin and eGFR than those with a normal QTc interval. There were no significant differences in sex; hypertension; current smoking; BMI; waist circumference; SBP; DBP; levels of sodium, potassium, and calcium; total cholesterol; TG; HDL-C; white blood cell (WBC) count, the number of diseased coronary arteries; the Gensini score; PCI; and the number of stents among the three groups. In addition, all of the participants had stable angina with a good thrombolysis in myocardial infarction (TIMI) flow grade. As a result, there were no significant deteriorations or differences between the TIMI flow grade before and after coronary angiography or angioplasty. Moreover, because all of our electrocardiographic parameters were collected before the examination, we believe that changes in TIMI flow grade change would not affect our results and conclusions.

We then performed multivariate logistic regression analysis to estimate the effects of plasma ADPN level and several other risk factors for arrhythmia in the presence of an abnormal QTc interval in the patients with stable angina. An abnormal QTc interval was positively associated with male sex and higher plasma ADPN level (Table II).

Pearson's correlation analysis indicated that plasma ADPN levels were positively correlated with age, heart rate, QTc interval, LVMI, creatinine, and hs-CRP and were negatively correlated with male sex, LVEF, BMI, waist circumference, current smoking, total cholesterol, TGs, LDL-C, albumin, and eGFR (Table III). Furthermore, age- and sex-adjusted ADPN levels were significantly positively associated with the heart rate, QTc interval, LVMI, creatinine, and hs-CRP and negatively associated with LVEF, waist circumference, current smoking, to-

tal cholesterol, TGs, LDL-C, albumin, and eGFR. However, there were no significant correlations among age- and sex-adjusted ADPN level and PR interval, QRS duration, QT interval, SBP, DBP, BMI, HDL-C, fasting glucose, HbA1c, and WBC count (Table III).

To investigate the impact of ADPN plasma level on the electrocardiographic and echocardiographic parameters, we divided the patients into three groups according to the tertile of sex-specific ADPN plasma level. There were significant trends in the associations among ADPN level and LVEF, LVMI, hs-CRP, heart rate, QRS duration, QTc interval, dyslipidemia, diabetes, CKD, LVH, LVSD, and all-cause mortality (*P* for trend <0.05) (Table IV). Furthermore, a Kaplan-Meier analysis revealed that the occurrence of all-cause mortality was the highest in the high-plasma ADPN level group (*P* = 0.003; Figure). Moreover, patients in the second and third tertiles of sex-specific ADPN had higher ORs for the presence of an abnormal QTc interval compared to those in the lowest tertile (1.69 [1.02-2.86] and 3.70 [2.13-6.57]). The ORs in the second and third tertiles of sex-specific ADPN level remained significant after adjusting for age, BMI, TGs, HDL-C, HbA1c, sodium, potassium, calcium, and WBC count (2.46 [1.08-5.96] and 3.05 [1.25-7.86]) (Table V).

Discussion

In the present study, we demonstrated that plasma ADPN levels were positively associated with heart rate, QTc interval, LVMI, and creatinine and negatively associated with LVEF, waist circumference, current smoking, total cholesterol, TGs, LDL-C, albumin, and eGFR. In addition, an increased plasma ADPN concentration was associated with an abnormal QTc interval, even in a fully adjusted model. Furthermore, patients in the highest (third) tertile of ADPN were three times more likely to have an abnormal QTc interval compared to those in the lowest tertile.

Table III. Association Between Plasma Adiponectin Levels and Clinical Laboratory Data

	Model 1		Model 2	
	<i>r</i>	<i>P</i> -value	β	<i>P</i> -value
Age	0.232	< 0.0001	-	-
Male sex	-0.169	0.0002	-	-
Heart rate	0.196	< 0.0001	0.162	< 0.0001
PR interval	0.011	0.820	-0.003	0.952
QRS duration	0.041	0.371	0.038	0.393
QT interval	0.023	0.610	-0.002	0.969
Corrected QT interval	0.246	< 0.0001	0.189	< 0.0001
LVEF	-0.271	< 0.0001	-0.242	< 0.0001
Left ventricular mass index	0.178	0.003	0.149	0.012
Systolic blood pressure	0.009	0.845	-0.030	0.510
Diastolic blood pressure	0.010	0.823	0.032	0.478
Body mass index	-0.154	0.001	-0.086	0.066
Waist circumference	-0.211	0.0001	-0.171	0.001
Current smoking	-0.170	0.0002	-0.116	0.019
Total-cholesterol	-0.140	0.002	-0.113	0.012
Triglycerides	-0.173	0.0001	-0.119	0.009
HDL-cholesterol	0.064	0.161	0.035	0.441
LDL-cholesterol	-0.163	0.0004	-0.146	0.001
Fasting glucose	0.025	0.583	0.012	0.784
HbA1c	0.047	0.351	0.055	0.259
Albumin	-0.259	< 0.0001	-0.214	< 0.0001
Creatinine	0.264	< 0.0001	0.254	< 0.0001
Estimated GFR	-0.295	< 0.0001	-0.298	< 0.0001
Hs-CRP	0.180	0.004	0.142	0.022
White blood cell count	-0.034	0.457	-0.007	0.870

Model 1: Pearson correlation coefficient. Model 2: Regression coefficient adjusted for age and sex. LVEF indicates left ventricular ejection fraction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR, glomerular filtration rate; and Hs-CRP, high-sensitivity C-reactive protein.

Table IV. Characteristics According to the Tertile of Sex-Specific Adiponectin Levels

Parameter	First tertile	Second tertile	Third tertile	<i>P</i> for trend
Adiponectin ($\mu\text{g/mL}$)	< 1.932 (men), < 3.308 (women)	1.932-7.795 (men), 3.308-11.425 (women)	> 7.795 (men), > 11.425 (women)	
Number	119	240	120	
LVEF (%)	63.2 $\pm$ 10.1	60.7 $\pm$ 12.3	51.7 $\pm$ 16.3	< 0.0001
LV mass index (g/m^2)	117.3 $\pm$ 31.4	130.8 $\pm$ 44.3	146.1 $\pm$ 49.3	0.0002
Hs-CRP (mg/L)	3.0 (1.1-8.1)	4.2 (1.4-11.0)	7.0 (1.8-28.3)	0.044
WBC count ($\times 10^9/\text{L}$)	8.525 $\pm$ 3.326	8.918 $\pm$ 3.305	8.237 $\pm$ 3.413	0.503
ECG parameters				
Heart rate (bpm)	73.0 $\pm$ 14.3	77.4 $\pm$ 20.4	82.9 $\pm$ 23.5	0.0001
PR interval (ms)	167.6 $\pm$ 27.7	170.6 $\pm$ 31.8	173.0 $\pm$ 32.0	0.201
QRS duration (ms)	93.6 $\pm$ 16.3	97.3 $\pm$ 20.2	100.2 $\pm$ 23.1	0.011
QT interval (ms)	396.9 $\pm$ 44.7	399.8 $\pm$ 46.3	403.4 $\pm$ 54.8	0.300
QTc interval (ms)	431.3 $\pm$ 45.6	444.9 $\pm$ 39.5	462.1 $\pm$ 42.1	< 0.0001
Hypertension, <i>n</i> (%)	87 (73.1)	177 (73.8)	92 (76.7)	0.530
Dyslipidemia, <i>n</i> (%)	47 (39.5)	103 (42.9)	63 (52.5)	0.006
Diabetes, <i>n</i> (%)	87 (73.1)	171 (71.3)	68 (56.7)	0.043
CKD, <i>n</i> (%)	52 (43.7)	137 (57.1)	92 (76.7)	< 0.0001
LVH, <i>n</i> (%)	34 (28.6)	110 (45.8)	67 (55.8)	0.002
LVSD, <i>n</i> (%)	16 (13.5)	39 (16.3)	55 (45.8)	< 0.0001
MACE, <i>n</i> (%)	54 (45.4)	106 (44.2)	61 (50.8)	0.388
All-cause mortality, <i>n</i> (%)	8 (6.7)	33 (13.8)	25 (20.8)	0.002

Data are expressed as mean $\pm$ SD, number (percentage), or median (interquartile range). LVEF indicates left ventricular ejection fraction; Hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; QTc, corrected QT; CKD, chronic kidney disease; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; and MACE, major adverse cardiovascular events.

Figure. Kaplan-Meier curves for survival estimate in patients with stable angina according to the tertile of sex-specific adiponectin (ADPN) levels. An ADPN level < 1.932 $\mu\text{g/mL}$ (men) and < 3.308 $\mu\text{g/mL}$ (women) was defined as low, that of 1.932-7.795 $\mu\text{g/mL}$ (men) and 3.308-11.425 $\mu\text{g/mL}$ (women) was defined as medium, and that > 7.795 $\mu\text{g/mL}$ (men) and > 11.425 $\mu\text{g/mL}$ (women) was defined as high.

Table V. Odds Ratios for the Presence of Abnormal Corrected QT Interval According to the Tertile of Sex-Specific Adiponectin Levels

Parameter	First tertile	Second tertile	Third tertile
Adiponectin ($\mu\text{g/mL}$)	< 1.928 (men), < 3.308 (women)	1.928-7.789 (men), 3.308-11.425 (women)	> 7.789 (men), > 11.425 (women)
Univariate	1.00	1.69 (1.02-2.86)	3.70 (2.13-6.57)
Multivariate*	1.00	2.46 (1.08-5.96)	3.05 (1.25-7.86)

Values presented are cut-offs of plasma adiponectin levels of all subjects, and odds ratios with 95% CIs. * Adjusted for age, body mass index, triglycerides, high-density lipoprotein cholesterol, HbA1c, sodium, potassium, calcium, and white blood cell count.

ADPN is an adipokine, which is synthesized in cardiac muscle cells and connective tissue cells within the heart.¹⁷⁾ ADPN has a critical signaling function in the heart, which is particularly important in patients with HF, and its beneficial cardioprotective effects have been verified. Clinical investigations have identified that ADPN deficiency (hypoadiponectinemia) is an independent risk factor for cardiovascular disease. In addition, animal studies have indicated that elevation of plasma ADPN by either pharmacological or genetic approaches alleviates obesity-induced endothelial dysfunction and hypertension and prevents atherosclerosis, myocardial infarction, and diabetic cardiomyopathy.³³⁾ However, both circulating total and high-molecular weight ADPN have been positively associated with mortality.³⁴⁾ Deleterious effects of ADPN on inflammatory processes under specific conditions have been reported, such as a proinflammatory effect by inducing chemokine production in colonic epithelial cells.³⁵⁾ Furthermore, Fayad, *et al.*³⁶⁾ reported that ADPN-deficient mice were protected from chemically induced colitis resembling inflammatory bowel disease and that ADPN infusion restored colon inflammation by inducing the local production of proinflammatory cytokines. Moreover, Liu, *et al.*³⁷⁾ reported that in rheumatoid arthritis, recombinant ADPN induced the synthesis of IL-6 and matrix metallo-

proteinase inhibitor 1 in human synovial fibroblasts through a p38 mitogen-activated protein kinase pathway. Finally, in cultured chondrocytes from patients with rheumatoid arthritis, ADPN stimulated the expression of vascular endothelial growth factor, monocyte chemoattractant protein 1, vascular cell adhesion molecule 1, and regulated on activation, normal T cell expressed and secreted (RANTES), all promoting inflammation.³⁷⁾ Taken together, these data indicate that under some chronic inflammatory conditions, ADPN, rather than being an anti-inflammatory factor, exacerbates inflammation in several tissues and cell types. In the present study, we demonstrated that the patients with an abnormal QTc interval had higher levels of hs-CRP and ADPN (Table I) and age- and sex-adjusted ADPN levels were also significantly positively associated with hs-CRP (Table II). Hence, our findings suggest that inflammatory activity as reflected by hs-CRP level was a strong etiologic factor for the higher levels of plasma ADPN in the patients with QTc prolongation. High levels of plasma ADPN have previously been demonstrated to be associated with HF, AF, coronary heart disease, and even mortality.¹⁶⁻¹⁸⁾ Furthermore, high levels of plasma ADPN have been directly associated with cardiac alterations such as LVH and both systolic and diastolic cardiac dysfunction.^{19,20,38)} Despite the strong evidence of the effect of

plasma ADPN concentration on cardiovascular diseases, only few reports investigated the underlying ADPN electrophysiological characteristics.

In 2010, Hoyda, *et al.*³⁹⁾ reported that ADPN decreased delayed rectifier potassium current in rat neurons by patch-clamp recordings. Whether the ADPN has a similar effect in cardiomyocyte remains unknown. However, a recent clinical report indicated the insulin resistance, which is associated with ADPN resistance, predicted future increase in Tpeak-Tend interval in the V5 lead of ECG in general population.⁴⁰⁾ These findings suggest that ADPN may play a role in the development of arrhythmogenesis in patients with stable angina but need more investigation.

In the present study, the patients with higher levels of plasma ADPN had a lower LVEF and higher LVMI compared to the other groups. A previous cohort study found that the ADPN level was positively associated with LVMI after multivariate adjustments in subjects with hypertension and insulin resistance.⁴¹⁾ Studies in patients on dialysis have also found a positive relationship between ADPN level and LVMI.^{42,43)} Moreover, ADPN is frequently increased in patients with congestive heart failure (CHF), and this is considered to be a strong predictor of mortality in patients with CHF.⁴⁴⁻⁴⁶⁾ Whether ADPN plays a protective or detrimental role in CHF remains unclear. However, when its beneficial effects on the cardiovascular system are considered, the increase in ADPN in patients with CHF may be part of a compensatory mechanism.⁴⁶⁾ Furthermore, in the present study, the patients with higher levels of plasma ADPN had higher rates of diabetes, CKD, LVH, and LVSD. In patients with chronic diseases, the disease process may outweigh the beneficial effects of ADPN, leading to its association with a worse clinical outcome.⁴⁷⁾

We also found that there were significant trends in the association between a high plasma ADPN level and all-cause mortality; however, the biology underlying this counterintuitive association is not known. A reasonable possibility is that increasing ADPN is a failed attempt to protect individuals at high risk of mortality. A possible reason for this failure may be ADPN resistance in metabolically active organs including the adipose tissue, the heart, skeletal muscles, vasculature, and the liver.⁴⁸⁾ Another possible explanation is that the ADPN paradox is driven by the direct and strong correlation between ADPN and natriuretic peptides, which are established risk factors for mortality.⁴⁹⁾

There are several limitations to this study. First, the cross-sectional design limits our ability to infer a causal relationship between increased plasma ADPN levels and QTc prolongation. Studies with long-term follow-up are needed to clarify the association between plasma ADPN and QTc prolongation. Second, although the heart rate and QT interval of all patients were measured by the same medical technician using identical methods, the QT intervals were measured using a computer-based method, and variability in the QT interval was not evaluated. Third, in accordance with the Taiwan Bureau of National Health Insurance guidelines, serum magnesium is not routinely measured in patients with stable angina; thus, no

magnesium data were available in the current study. As previous studies have reported an association between hypomagnesemia and atrial and ventricular arrhythmias, low levels of serum magnesium could also be a risk factor for sudden cardiac death.^{50,51)} However, no association has been reported between serum magnesium levels and QTc interval.²⁹⁾ Fourth, we could not analyze our data stratified by sex because of the small sample size. Nevertheless, we assessed the relationship between the ADPN level and clinical characteristics including ECG parameters and the odds ratio for QTc prolongation in ADPN tertiles according to the sex-specific tertiles of ADPN. Fifth, we chose individuals with stable angina for this study; thus, the results of the present study might not be generalizable to other populations. Furthermore, whether ADPN is associated with the expression of cardiac ion channels, cardiomyocyte electrophysiology, and the underlying mechanism are still unclear. Further investigations are warranted to elucidate these issues.

In conclusion, we demonstrated that a prolonged QTc interval in patients with stable angina was correlated with an elevated ADPN level. The mechanisms by which the ADPN level and the QTc interval are linked remain to be investigated.

Acknowledgments

We appreciate the assistance of the staff and members of the heart care teams for their assistance with various measurements and other organizational aspects of this study.

Disclosure

Conflicts of interest: The authors have no conflicts of interest to disclose.

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