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Original Research

Serum Adropin Level in Patients with Isolated Coronary Artery Ectasia

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ABSTRACT

Objective: Isolated coronary artery ectasia (iCAE) is characterized by localized or diffuse dilatation of the coronary arteries, and the exact mechanism underlying iCAE is unclear. However, endothelial dysfunction is related to iCAE. Adropin has a regulatory effect in the coronary artery endothelium. This study aimed to determine the relationship of adropin level to iCAE.

Methods: Fifty patients with iCAE and 32 age- and sex-matched control subjects with normal coronary angiography (CAG) findings were selected from 4546 patients who underwent CAG between July 2019 and October 2019. Blood sample for adropin analysis were collected just before CAG.

Results: No significant difference was found between groups in terms of baseline characteristics and laboratory parameters. The mean adropin level in patients with iCAE was significantly lower than that in control subjects (0.33±0.35 vs. 0.55±0.35 ng/mL, p<0.001). In receiver operating characteristic analysis, the cut-off value of adropin ≤0.341 had 76.0% sensitivity and 84.37% specificity for predicting iCAE (area under the curve: 0.839, p<0.001). Multivariate analysis included age, left ventricular ejection fraction, and adropin level, which showed that adropin (per 1 ng/dL decrease) (odds ratio: 0.973 [0.956–0.990]; p=0.002) was independently associated with iCAE.

Conclusion: The present study showed that adropin level is significantly lower in patients with iCAE patients and is independently associated with iCAE.

Keywords: Adropin, coronary ectasia, endothelial dysfunction

INTRODUCTION

Coronary artery ectasia (CAE) is characterized by localized or diffuse dilatation of the coronary arteries. CAE is determined as the ratio of dilated segment of the coronary artery to the adjacent normal segment of >1.5 (1). The prevalence of CAE was 1.2%– 4.9% in different studies (1-3). The exact mechanism underlying CAE is unclear. However, atherosclerosis, inflammation, and endothelial dysfunction have been suggested to be possible mechanisms (2,3). The possible mechanism in almost half of patients with CAE is atherosclerosis. However, in a small number of patients, CAE occurs without significant atherosclerosis, which is called isolated CAE (iCAE). The prevalence of iCAE is 0.1%–0.79% in studies (1-3). The endothelium plays an important role in the maintenance of vascular homeostasis, and dysfunction of the endothelium is related to CAE (4, 5).

Adropin is a protein that participates in the maintenance of energy homeostasis and insulin response. Moreover, adropin has vascular effect by increasing the eNOS protein levels and mRNA expression in the coronary artery endothelium (6). Hence, adropin has a regulating effect in the coronary artery endothelium. We aimed to determine the relationship of adropin level to CAE.

METHODS

Patients

Between July 2019 and October 2019, all consecutive patients (n=4546) underwent elective coronary artery angiography (CAG) for angina pectoris, or significant myocardial ischemia was evaluated using non-invasive stress test in our center. Of those, 132 (2.9%) patients were diagnosed with CAE. Patients with acute coronary syndrome, atherosclerotic stenosis in the coronary arteries, left ventricular ejection fraction (LVEF) <40%, acute heart failure, severe valvular disease or significant left ventricular hypertrophy (septal thickness> 15 mm) in echocardiography, previously known inflammatory/autoimmune disorders, malignancy, and chronic infection were excluded from the study. After exclusion criteria, 50 (37.8%) patients with iCAE were included. The control subjects were 32 age- and sex-matched healthy subjects with normal coronary arteries. Detailed medical characteristics of patients and control subjects were recorded after CAG. All participants signed informed consent forms before study inclusion. The local ethic committee of Adana Health Practice and Research Center approved this research (2019-518).

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Hypertension (HT) was defined as systolic blood pressure (BP) ≥140 mmHg (≥130 mmHg for diabetes mellitus [DM]) and/or diastolic BP ≥90 mmHg (≥80 mmHg for DM), and use of antihypertensive drugs.

Type 2 DM was defined as use of anti-diabetic medications or fasting blood glucose of ≥126 mg/dL. Hyperlipidemia was defined as total cholesterol level ≥200 mg/dL and/or use of lipid-lowering medications. Family history was defined as history of coronary artery disease or sudden cardiac death in any first-degree relative (male <55 years or female <65 years).

Angiographic Analysis

Routine coronary angiography was performed for all patients, and all images were recorded with coronary angiography digitized system (Siemens, Munchen, Germany). All CAG images were recorded and analyzed by two experienced interventional cardiologists blinded to the patient's clinical status. CAE was determined as exceeding coronary artery dilatation 1.5-fold than the normal segment of the coronary artery.

Blood Sample Collection and Analyses

Venous blood specimens were collected in citrate tubes for adropin analysis just before the CAG procedure. The specimens were centrifuged for 30 min at 4000 cycles. Plasma was placed in an Eppendorf tube and kept at –80°C until the assay was performed. Frozen serum was thawed slowly for 24 h, and the adropin levels were measured after the samples reached room temperature. Serum adropin levels were analyzed using a commercially available enzyme-linked immunosorbent assay kit (Cusabio Biotech Co., Wuhan, China).

Statistical Analyses

Continuous variables with normal distribution were described as mean (±SD). Variables with normal and not normal distribution were compared using Student t-test and Mann Whitney U-test, respectively. Categorical variables are presented as numbers and percentages and compared using the chi-squared or Fisher exact test. The receiver operating characteristics (ROC) was used to determine the sensitivity and specificity of adropin cut-off values for iCAE.

Binary logistics regression analysis was performed to determine the variable associated with iCAE, Statistical Package for the Social Sciences (SPSS 20.0) for Windows (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis, and $p<0.05$ was considered statistically significant.

RESULTS

The study included 50 patients (58.7±11.2 years, 32.0%, n=16 women) and 32 (55.6±8.2 years, 43.8%, n=14 women) control subjects.

Main Points:

- The exact mechanism underlying isolated coronary artery ectasia is unclear. In present study we showed that Adropin, which has a regulatory effect in the coronary artery endothelium, level is significantly lower in patients with isolated coronary artery ectasia.

Baseline medical and demographic characteristics of the patients and control subjects are summarized in Table 1. Demographic and medical characteristics of study groups were similar. The laboratory parameters of the groups are summarized in Table 2.

No significant difference was found between the groups in terms of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, hemoglobin, fasting blood glucose, C-reactive protein, and troponin level. Compared with the control subjects, the mean adropin level was significantly lower in iCAE (0.55±0.35 ng/mL vs. 0.33±0.35, $p<0.001$) (Figure 1). The correlation between adropin level and demographic and laboratory parameters are shown in Table 3. A statistically significant but weak correlation was found between adropin level and mean platelet volume and LVEF. In the ROC analysis, a cut-off value

Table 1. Baseline characteristics of the study population

Variables	iCAE (+) (n=50)	Control (n=32)	p
Age, years	58.7±11.2	55.6±8.2	0.183
BMI (kg/m^2)	24.8±5.7	25.8±6.6	0.515
Female, % (n)	32.0 (16)	43.8 (14)	0.281
Diabetes mellitus, % (n)	38.0 (19)	34.4 (11)	0.740
Hypertension, % (n)	62.0 (31)	59.4 (19)	0.812
Smoker, % (n)	46.0 (23)	43.6 (14)	0.842
Family history of coronary artery disease, % (n)	10.0 (5)	12.5 (4)	0.724
Systolic blood pressure (mmHg)	122±19	116±14	0.166
Diastolic blood pressure (mmHg)	76±10	73±13	0.259
LVEF, %	56.1±3.9	54.7±7.6	0.241

Figure 1. Comparison of adropin level of study groups

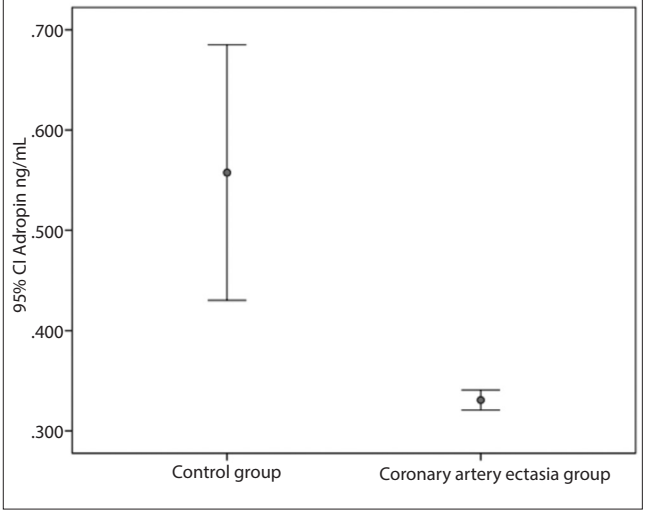

Table 2. Comparison of laboratory parameters of the study groups

Parameters	iCAE (+) (n=50)	Control (n=32)	p
Hemoglobin, g/dL	13.7±1.8	13.2±1.5	0.192
Hematocrit, %	40.2±5.1	39.4±4.1	0.406
White blood cell count, $\times 10^3$/mL	8.3±2.2	8.4±2.4	0.960
Platelet count, $\times 10^3$/mL	259±70	269±50	0.514
Lymphocyte count, $\times 10^3$/mL	2.7±1.2	2.6±0.9	0.752
Neutrophil count, $\times 10^3$/mL	4.6±1.5	4.7±1.5	0.667
Monocyte count, $\times 10^3$/mL	0.7±0.2	0.7±0.1	0.991
Mean platelet volume, fL	8.59±0.9	8.84±1.02	0.235
Neutrophil/lymphocyte ratio	1.95±1.01	1.87±0.5	0.725
Glucose (mg/dL)	121±40	134±46	0.184
Creatinine (mg/dL)	0.81±0.16	0.78±0.15	0.421
C-reactive protein (mg/L)	2.83±2.9	2.1±1.7	0.235
CK-MB (ng/mL)	1.44±1.1	1.36±0.98	0.727
Troponin (ng/mL)	7.1±3.3	5.7±2.2	0.378
Total cholesterol (mg/dL)	209±47.8	212±34	0.744
HDL-cholesterol (mg/dL)	43±9.7	45±8.3	0.396
LDL-cholesterol (mg/dL)	141±43	147±26	0.546
Triglyceride (mg/dL)	190±94	184±97	0.780
Adropin (ng/mL)	0.33±0.35	0.55±0.35	<0.001

Figure 2. Receiver operating characteristic analysis of adropin level

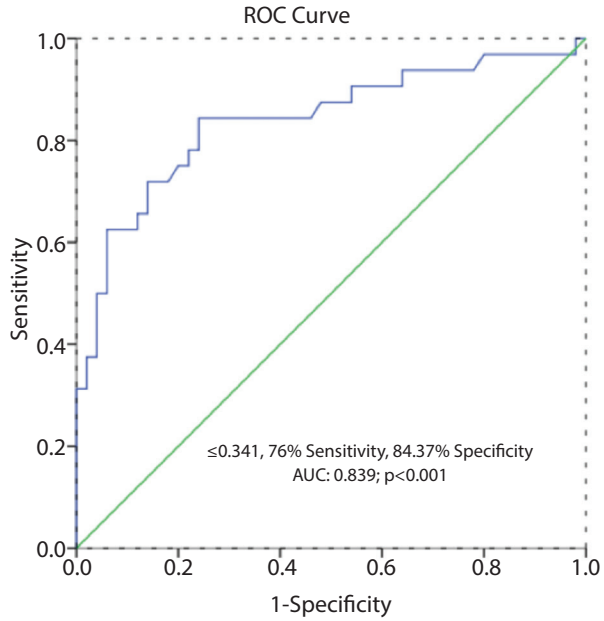

Table 3. Correlation between serum adropin level and baseline characteristics and laboratory parameters of patients

	Adropin level	
Variable	**r**	**p**
Age	−0.167	0.133
BMI	−0.122	0.901
Female	−0.10	0.376
Diabetes mellitus	0.041	0.713
Hypertension	−0.03	0.817
Smoker	−0.12	0.282
Family history of coronary artery disease	0.016	0.883
Systolic blood pressure (mmHg)	0.02	0.862
Diastolic blood pressure (mmHg)	0.104	0.354
LVEF	−0.343	0.002
Hemoglobin	−0.134	0.231
Platelet count	0.098	0.383
Lymphocyte count	−0.058	0.605
Neutrophil/lymphocyte ratio	−0.081	0.470
Mean platelet volume	0.219	0.048
Glucose	0.071	0.526
Creatinine	−0.118	0.292
C-reactive protein	−0.090	0.424
Troponin	0.090	0.422
Total cholesterol	−0.063	0.571
HDL-cholesterol	0.040	0.723
LDL-cholesterol	0.044	0.692
Triglyceride	−0.066	0.554

of adropin ≤0.341 had 76.0% sensitivity and 84.37% specificity for predicting iCAE (area under the curve, 0.839; 95% confidence interval [CI], 0.743–0.935; p<0.001] (Figure 2). Univariate and multivariate logistic regression analyses were performed to determine the risk factors of iCAE, and the results are summarized in Table 4. Univariate analysis showed that LVEF (OR, 1.192; 95% CI, 1.053–1.349; p=0.005) and adropin (OR, 0.976; 95% CI, 0.962–0.990; p<0.001) were predictors of iCAE. The multivariate analysis included age, LVEF, and adropin and showed that adropin (per 1 ng/mL decrease) (OR, 0.973 [0.956–0.990]; p=0.002) was independently associated with iCAE.

DISCUSSION

In our study, plasma adropin level was significantly decreased in patients with iCAE compared with the healthy control subjects. Decreased serum adropin level was also independently associated with iCAE.

Table 4. Logistic regression analysis of possible predictors for isolated coronary artery ectasia

Analysis		Univariate		Multivariate
Variables	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**
Age	0.183	1.031 (0.986–1.078)		
Female	0.283	1.653 (0.661–4.135)		
Body mass index (per 1 kg/m^2 decrease)	0.496	0.975 (0.905–1.050)		
LVEF (per 1% decrease)	0.005	1.192 (1.053–1.349)		
Mean platelet volume	0.234	0.747 (0.463–1.207)		
Glucose	0.186	0.993 (0.983–1.003)		
Systolic blood pressure	0.168	1.020 (0.992–1.048)		
Hemoglobin	0.193	1.193 (0.915–1.557)		
C–reactive protein	0.248	1.147 (0.909–1.446)		
Adropin (per 1–ng/dL decrease)	<0.001	0.976 (0.962–0.990)	0.002	0.973 (0.956–0.990)

CAE is characterized by localized or diffuse dilatation of the coronary arteries with 1.2%–4.9% prevalence in different CAG studies. Although the exact mechanism underlying of CAE remain unclear, different mechanisms have been suggested.

CEA is considered a variant of atherosclerosis, mainly due to an extensive exaggerated positive remodeling of the coronary artery (7). The most probable mechanism for this inappropriate remodeling is the thinning of the tunica media associated with enzymatic degradation of the extracellular matrix and chronic inflammation (8, 9).

Markis et al. (10) suggested that CAE is caused by tunica media damage. Another potential causative mechanism is chronic overstimulation of the endothelium by nitric oxide (NO). Although nearly half of patients with CAE have atherosclerosis as the underlying disease, in the other half, CAE develops without atherosclerosis and is defined as iCAE (11, 12). The most important underlying cause of patients with iCAE is chronic inflammation and endothelial dysfunction as mentioned above. Several studies have previously shown a relationship between inflammation markers, such as plasma interleukin-6, plasma soluble adhesion molecules (ICAM-I, VCAM-I, and E-selectin), and C-reactive protein, and iCAE development (12-15). In addition, Kocaman et al. (16) showed that monocyte, leukocyte, and neutrophil levels in patients with iCAE were significantly higher than those in normal controls. Doğduş et al. (11) have recently determined that the increase may have occurred in the early pathogenesis of iCEA. The vascular endothelium has many different mechanisms to maintain normal vascular physiology. NO is a potent endogenous vasodilator and has an important role in flow-mediated vasodilation (17-20). NO also suppresses vascular smooth muscle proliferation and inhibits platelet adhesion to the endothelium (18, 19). Inflammatory cell-mediated NO production results in high NO levels, and toxin production degrades elastin and disrupts the extracellular matrix. Decreased NO level in the vascular endothelium is related to vasoconstriction, ischemia, and atherosclerosis. In addition, Gurlek et al. (21) have shown that the NO level in patients with CAE patients was significantly lower than that in normal subjects.

Adropin is a recently identified protein encoded by energy homeostasis-associated gene (*Enho*) and mainly expressed in the heart, brain, liver, and coronary endothelial cells (22). Adropin is involved in regulating lipid metabolism, improving insulin resistance, protecting vascular endothelial cells, and has anti-inflammatory effects. The positive effects of adropin can be achieved by increasing endothelial NO synthase expression. Studies have shown that decreased serum adropin level is associated with endothelial dysfunction (20, 23). Moreover, Decreased adropin levels may play a role in the cause and progression of atherosclerosis by weakening the protective effect of the endothelium (6, 23-25). Yu et al. (26) showed that serum adropin levels in patients with acute coronary artery disease were significantly lower than those in healthy controls. Similarly, Demircelik et al. (27) showed that the adropin level in patients with occluded saphenous vein graft is lower than that in those with potent saphenous graft. In summary, adropin is associated with vascular endothelial function, inflammation, and atherosclerosis. Similarly, iCAE is associated with endothelial dysfunction and inflammation. Because adropin and iCAE share similar pathogenic mechanisms, we hypothesized that adropin level and iCAE may be associated. Our results supported our hypothesis and showed that adropin level in iCAE patients is lower than that in normal control subjects. Moreover, adropin is an independent predictor for iCAE.

Our study has many limitations. First, the study primarily has a cross-sectional design and relatively small population and is single center. Thus, the molecular mechanism underlying the relationship between adropin and iCAE could not be clarified. Second, the correlation between adropin and other inflammatory markers, such as P-selectin and interleukin-6, was not evaluated. Third, because of the lack of follow-up, the effect of adropin in the clinical outcomes was not evaluated in patients with iCAE.

CONCLUSION

Our study showed that adropin level is significantly lower in patients with iCAE, and adropin is independently associated with iCAE.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Adana Health Practice and Research Center approved this research. / (2019-518).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.K.; Design - M.K.; Supervision - M.K.; Resources - F.Y.; Materials - M.K., F.Y.; Data Collection and/or Processing - F.Y.; Analysis and/or Interpretation - M.K., F.Y., M.K.; Literature Search - M.K., F.Y., M.K.; Writing Manuscript - M.K.; Critical Review - M.K.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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