Association between serum adropin level and burden of coronary artery disease in patients with non-ST elevation myocardial infarction

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Abstract

Objective: Previous studies revealed the relationship between stable coronary artery disease (CAD) and serum adropin level, but this relationship has not been investigated in patients with non-ST segment elevation myocardial infarction (NSTEMI). The present study is an analysis of the relationship between adropin and severity of CAD assessed based on SYNTAX score in patients with NSTEMI.

Methods: A total of 109 participants, 80 patients with NSTEMI and 29 healthy individuals, were prospectively enrolled in the study. Patients with NSTEMI were divided to 2 groups: high SYNTAX score (≥32) (35 patients) and low SYNTAX score (<32) (45 patients). Adropin level was measured from blood serum samples using enzyme-linked immunosorbent assay test.

Results: Patients with NSTEMI and high SYNTAX score had significantly lower serum adropin level (2357.30 pg/mL±821.58) compared to NSTEMI patients with low SYNTAX score (3077.00 pg/mL±912.86) and control group (3688.00±956.65). Adropin cut-off value for predicting high SYNTAX score on receiver-operating characteristic curve analysis was determined to be 2759 pg/mL, with a sensitivity of 63% and a specificity of 57%. Adropin was an independent predictor for high SYNTAX score (odds ratio=0.999; 95% confidence interval: 0.998–1.000; p=0.007).

Conclusion: Adropin could be an alternative blood sample value for predicting severity of CAD. *(Anatol J Cardiol 2017; 17: 119-24)*

Keywords: acute coronary syndrome, adropin, SYNTAX score

Introduction

SYNTAX score is an angiographic scoring system that defines grade and complexity of coronary artery disease (CAD) (1, 2). It has been confirmed in numerous studies that patients with a relatively high SYNTAX score have poor outcomes, and that the score is an independent predictor of major advanced cardiovascular outcomes (MACE) for percutaneous coronary intervention (PCI) (3, 4).

Adropin has been identified recently as a regulatory protein that participates in the regulation of energy homeostasis and insulin response (5). Kumar et al. (6) observed adropin in mice and demonstrated that adropin has protective effects on cardiac system (7). There is growing evidence suggesting that adropin is a potential regulator of cardiovascular functions and plays a protective role in pathogenesis and development of cardiovascular diseases (8). Significant proliferation, migration, capillary-like tube formation, and upregulation of the expression of endothelial nitric oxide synthase were observed in adropin-treated endothelial cells (8). In a recent study, it was found that patients with stable ischemic heart disease have lower adropin concentrations (9). Also, Demirçelik et al. (10) reported that adropin level is lower in patients with late saphenous vein graft occlusion.

This study evaluated the relationship between adropin level and severity of CAD according to SYNTAX score in patients with non-ST segment elevation myocardial infarction (NSTEMI).

Methods

Study population

Eighty patients who underwent coronary angiography (CA) for NSTEMI at Türkiye Yüksek İhtisas Training and Research Hospital and 29 patients with normal coronary artery (NCA) were enrolled in the study from November 2015 to January 2016. Patients with previous coronary artery bypass grafting (CABG) were excluded since SYNTAX score is suitable only for patients with native coro-

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nary artery lesions. Patients with active infection, chronic inflammatory diseases, severe hepatic or renal dysfunction, and malignancy were also excluded from the study. Presentation with acute chest pain or overwhelming shortness of breath, with no ST-elevation but with classic rise and fall of at least 1 cardiac enzyme (troponin or creatine kinase-myocardial band) was defined as NSTEMI. Patients with NCA were referred to coronary angiography as result of positive stress test (exercise stress test or myocardial-perfusion scintigraphy test) or high clinical suspicion of CAD (e.g., patients with strong family history of CAD or early death with or without associated risk factors, and patients with unexplained chest pain after careful clinical and laboratory evaluation if there was suspicion of ischemic heart disease) during outpatient clinic visit. NCA is defined as no visible disease or luminal irregularity (less than 50%) as judged visually on CA. The study was approved by the local Ethical Committee and all patients provided written, informed consent.

Coronary angiography

CA was performed using the Judkins technique (Siemens Axiom Artis Zee 2011; Siemens Healthcare, Erlangen, Germany) through femoral or radial artery. Each coronary artery was displayed in at least 2 different plane images. PCI procedures were performed using standard techniques. According to baseline CA, SYNTAX score was calculated for all patients by 2 experienced interventional cardiologists who were unaware of patients' clinical or laboratory results. SYNTAX score was determined for all coronary lesions with >50% diameter stenosis in a vessel >1.5 mm based on SYNTAX score calculator 2.1 (www.syntaxscore.com). NSTEMI patients were divided into 2 groups: high SYNTAX score (≥32) (35 patients) and low SYNTAX score (<32) (45 patients).

Reproducibility

To define intra-observer variability, 15 patients were selected at random from the study group. Measurements were repeated under the same basal conditions. Reproducibility of SYNTAX score by CA was assessed with coefficient of variation between measurements. Intra-observer variability was 5.5% for SYNTAX score.

Laboratory measurements

Samples of peripheral venous blood were drawn from antecubital vein on admission. Baseline creatinine concentration, white blood cell (WBC) count, platelet count, and hemoglobin level were measured. On the first morning after admission, lipid profile, high sensitivity C-reactive protein (hs-CRP), and other biochemical parameters were measured using standard methods. Baseline and peak levels of creatinine kinase myocardial band and troponin level were also recorded.

Blood samples to be used for adropin measurement were centrifuged immediately and serum samples were stored at -80°C until the day of analysis. Serum adropin measurement was carried out using human adropin enzyme-linked immunosorbent assay commercial kit (Catalog no. 201–12–3107, limit determination 5–10000 pg/mL; Sunred Biological Technology Co., Shanghai, PRC) as recommended by the manufacturer's protocol.

Statistical analysis

Data were analyzed using SPSS version 18.0 statistics package (SPSS Inc., Chicago, Il, USA). Continuous variables were reported as mean±SD and categorical variables were reported as percentages and counts. Student's t-test was used for comparison of normally distributed variables and Mann-Whitney U test was used for non-normally distributed variables if 2 groups existed. One-way analysis of variance test was used to compare normally distributed variables between 3 groups. Tukey test was used for posthoc analysis. Categorical variables were compared by χ^2 test or Fisher's exact test, as appropriate. Pearson's correlation coefficients were used to assess strength of relationship between continuous variables and Spearman correlation analysis was performed for non-continuous and categorical variables. Univariate and multiple models consisted of SYNTAX ≥32 score and variables (hs-CRP, adropin, left ventricle ejection fraction, dyslipidemia, WBC, smoking status, high-density lipoprotein [HDL] cholesterol). In all analyses, p value of <0.05 was considered statistically significant.

Results

Baseline clinical and angiographic characteristics of the study population are shown in Table 1. Age, gender, body mass index, blood pressure (systolic and diastolic), diabetes mellitus (DM), and smoking status data were not statistically significant between groups. Compared with low SYNTAX group (score <32) patients, high SYNTAX group (score ≥32) patients had significantly larger number of previous myocardial infarction (MI), multi-vessel coronary involvement, chronic total occlusion, CABG procedure, and collateral vessels , and fewer stent implantations (p=0.015, p<0.001, p<0.001, p<0.001, p=0.018, and p<0.001, respectively).

Biochemical, hematological and serum adropin measurements of the study population are provided in Table 2. There was no statistically significant difference between groups other than WBC (p=0.003) and HDL cholesterol (p=0.001). Present study demonstrated that NSTEMI patients with a high SYNTAX score (score >32) had significantly lower serum adropin levels (2357.30 pg/mL±821.58) compared to NSTEMI patients with a low SYNTAX score (score <32) (3077.00 pg/mL±912.86) and control group (3688.00 ng /mL±956.65). There was statistically significant difference between all groups in terms of adropin levels (p<0.001). In addition, there was statistically significant difference between high SYNTAX score group and low SYNTAX score group (p=0.003), high score group and controls (p=<0.001), and low score group and controls (p=0.016).

Table 1. Baseline clinical and angiographic characteristics of the study population

Variable	NSTEMI SYNTAX score ≥32 (n=35)	NSTEMI SYNTAX score <32 (n=45)	NCA (n=29)	P*	P§	Pβ	Pα
Age, years	62.94±9.49	62.29±8.25	58.90±10.64	0.187			
BMI, kg/m^2	30.03±5.67	30.09±4.99	29.90±6.13	0.989			
Female, n (%)	12 (34.3%)	11 (22.4%)	8 (27.6%)	0.622			
Systolic blood pressure, mm Hg	136.48±7.35	135.66±10.87	136.79±5.75	0.843			
Diastolic blood pressure, mm Hg	84.65±6.36	84.60±9.53	85.00±4.51	0.973			
Diabetes mellitus, n (%)	13 (37.1%)	10 (22.2%)	7 (24.1%)	0.298			
Current smoking, n (%)	17 (48.6%)	28 (62.2%)	8 (27.6%)	**0.014**			
Dyslipidemia, n (%)	17 (48.6%)	21 (46.7%)	6 (20.7%)	**0.041**			
Previous MI, n (%)	5 (14.3%)	11 (24.4%)	0 (0%)	**0.015**			
Multi-vessel disease, n (%)	32 (91.4%)	30 (66.7%)	0 (0%)	**<0.001**			
LVEF, %	53.92±10.86	51.82±8.89	58.04±6.85	**0.035**	0.619	0.24	**0.026**
Chronic total occlusion, n (%)	13 (37.1%)	7 (15.6%)	0 (0%)	**<0.001**			
Stent implantation, n (%)	15 (42.9%)	29 (64.4%)	0 (0%)	**<0.001**			
Decision for CABG, n (%)	15 (42.9%)	5 (11.1%)	0 (0%)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Collateral vessel, n (%)	10 (28.6%)	4 (8.9%)	0 (0%)	**0.018**			
SYNTAX score	37.77±3.66	17.88±7.13	0±0	**<0.001**			

BMI - body mass index; CABG - coronary artery bypass grafting; LVEF - left ventricular ejection fraction; MI - myocardial infarction; NCA - normal coronary artery; NSTEMI - non-ST segment elevation myocardial infarction. ***P**** - ***P*** value between all groups; ***P*§ - ***P*** value between SYNTAX score <32 and SYNTAX score ≥32; ***P*^{β} - ***P*** value between SYNTAX score ≥32 and controls; ***P*^{α} - ***P*** value between SYNTAX score <32 and controls

Table 2. Biochemical and hematological measurements of the study patients

Variable	NSTEMI SYNTAX score ≥32 (n=35)	NSTEMI SYNTAX score <32 (n=45)	NCA (n=29)	P*	P§	Pβ	Pα
WBC count, x10^9/L	9.20±2.15	8.81±2.12	7.52±1.59	**0.003**	0.668	**0.003**	0.024
Platelet count, x10^9/L	238.91±70.66	248.83±74.45	249.46±66.39	0.787			
Hemoglobin, g/dL	13.79±1.63	13.82±1.76	13.37±1.28	0.494			
Serum glucose, mg/dL	151.92±72.33	131.08±47.76	133.75±45.02	0.234			
Creatinine, mg/dL	0.99±0.26	1.12±0.78	0.91±0.113	0.234			
Peak CK-MB, U/L	45.70 (15–229)	37.46 (0–131)	–	0.488			
Peak troponin-T, ng/mL	4.51 (0–34.7)	5.27 (0.09–31.00)	–	0.884			
Total cholesterol, mg/dL	199.71±49.03	188.44±55.27	176.20±45.28	0.237			
HDL-cholesterol, mg/dL	47.65±12.56	46.18±10.11	58.54±16.91	**0.001**	0.876	**0.006**	**0.001**
LDL-cholesterol, mg/dL	118.96±42.78	112.18±45.09	98.75±37.77	0.215			
Triglyceride, mg/dL	174.84±113.24	150.76±91.30	147.13±79.68	0.479			
Hs-CRP, mg/L	4.02±0.81	3.32±1.23	1.58±0.59	**<0.001**	**0.005**	**<0.001**	**<0.001**
Glomerular filtration rate, mL/min/1.73 m^2	75.31±17.10	76.64±20.21	80.30±9.11	0.706			
Adropin, pg/mL	2357.30±821.58	3077.00±912.86	3688.00±956.65	**<0.001**	**0.003**	**<0.001**	**0.016**

CK-MB - creatine kinase-myocardial band; HDL - high density lypoprotein; hs-CRP - high sensitivity C-reactive protein; LDL - low density lypoprotein; NCA - normal coronary artery; NSTEMI - Non ST-segment elevation myocardial infarction; WBC - white blood cell. ***P**** - ***P*** value between all groups; ***P*§ - P value between SYNTAX score <32 and SYNTAX score ≥32; ***P*** - ***P*** value between SYNTAX score 32 and controls; ***P*** - ***P*** value between SYNTAX score <32 and controls

As demonstrated in Figure 1, serum adropin level was negatively correlated with SYNTAX score (r=-0.442, p<0.001). Univariate and multiple linear regression analysis were performed for predictors of SYNTAX ≥32 score, and can be seen in Table 3. In univariate regression analysis, hs-CRP (odds ratio [OR]=1.874; 95% confidence interval [CI]: 1.179–2.979; p=0.008) and adropin

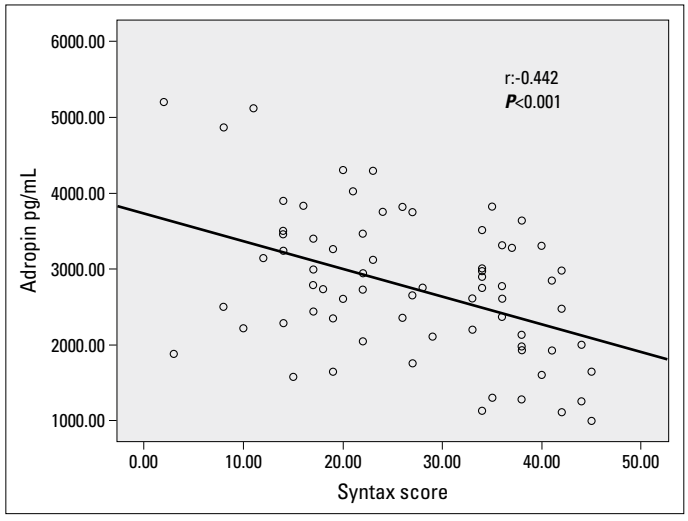

Figure 1. The correlation between adropin level and SYNTAX score

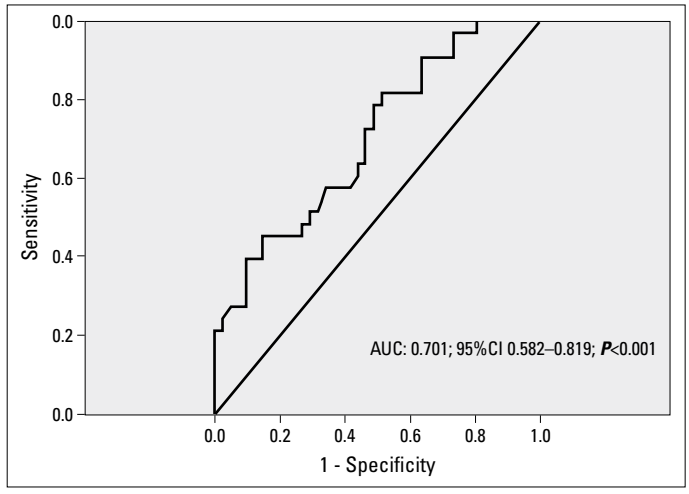

Figure 2. Receiver operating characteristic curves of serum adropin level for predicting high SYNTAX score

Table 3. Univariate and multiple linear regression analysis showing the predictors for SYNTAX ≥32 score

	Univariable		Multivariable	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Hs-CRP	1.874 (1.179–2.979)	0.008	1.652 (0.810–3.371)	0.67
Adropin	0.999 (0.998–1.000)	0.002	0.999 (0.998–1.000)	0.007
Left ventricle EF	1.023 (0.972–1.077)	0.386	–	–
Dyslipidemia	0.926 (0.383–2.244)	0.866	–	–
White blood cell	1.091 (0.883–1.349)	0.419	–	–
Smoking	1.744 (0.712–4.272)	0.224	–	–
HDL cholesterol	1.012 (0.971–1.055)	0.571	–	–

CI - confidence interval; OR - odds ratio; EF - ejection fraction; hs-CRP - high sensitive C-reactive protein; HDL - high density lipoprotein

(OR=0.999; 95% CI: 0.998–1.000; p=0.002) were associated with SYNTAX score. After multiple linear regression analysis, lower serum level of adropin was the only independent predictor of high SYNTAX score in NSTEMI patients (OR=0.999; 95% CI: 0.998–1.000; p=0.007).

The adropin cut-off value at admission for predicting high SYNTAX score in the entire study population based on receiver-operating characteristic curve analysis was determined to be 2759 pg/mL, with a sensitivity of 63% and a specificity of 57% (area under the curve: 0.701; 95% CI: 0.582–0.819; p<0.001) (Fig. 2).

Discussion

The current study demonstrated that serum adropin level was significantly lower in patients with NSTEMI than patients with NCA. Also, serum adropin level was lower in patients with high SYNTAX score compared to low SYNTAX score. Furthermore, decreased serum adropin level was negatively correlated with SYNTAX score. Low serum adropin level was independent predictor of high SYNTAX score in patients with NSTEMI.

NSTEMI is one of the most common presentations of patients with acute coronary syndromes. Although in-hospital mortality in patients with NSTEMI is lower than those with ST-segment elevation, 6-month mortality rate is similar. Moreover, 4-year mortality in patients with NSTEMI is two times higher than patients with ST-segment MI (11–13). Intensive medical treatment and invasive procedures have been successful in decreasing morbidity and mortality of NSTEMI (12). However, severity of CAD in coronary angiography is leading factor in determining the most useful treatment strategy.

SYNTAX score is a visual angiographic score that represents CAD complexity by taking into account the number of lesions and their functional and anatomic components including location, presence of bifurcations, tortuosity, total occlusions, collaterals, thrombus, and calcification. It has been shown to be useful for decision-making about optimal revascularization strategy, i.e., PCI or CABG, among patients with CAD. High SYNTAX scores are indicative of more complex disease and related to a troublesome therapeutic challenge. Patients with high SYNTAX score have increased rate of major adverse cardiac or cerebrovascular events (14–16). In the present study, patients with high SYNTAX (≥32) score have more chronic total occlusion, decision to perform CABG and collateral vessels than patients with low-moderate SYNTAX (<32) score.

Adropin is a recently identified bioactive peptide hormone that is encoded by the energy homeostasis associated (Enho) gene and is released by the brain, liver, heart, and coronary artery (6). It has a critical role in energy metabolism, homeostasis, and modulation of insulin sensitivity and obesity (6, 8, 17). A recent study showed that adropin is released in coronary artery endothelial cells and plays a crucial role in endothelial protec-

tion in mice (6). Ignarro et al. (18) also demonstrated that serum adropin could raise the expression of endothelial nitric oxide synthase in the endothelium. Decreased serum adropin level is associated with reduced nitric oxide (NO) bioavailability in the endothelium. Reduced NO bioavailability is a cardinal feature of endothelial dysfunction that is predictor of atherosclerosis (8). Gözal et al. (19) showed that adropin concentration is reduced in children with obstructive sleep apnea who exhibit endothelial dysfunction. Also, Topuz et al. (20) found that adropin level was lower in group with the endothelial dysfunction. All these findings suggest that adropin may be a new and effective marker for noninvasive evaluation of endothelial functions. Endothelial dysfunction has also play role in the pathogenesis of cardiac syndrome X (CSX), according to these data. Çelik et al. (21) demonstrated that lower serum adropin levels are associated with CSX.

Endothelial dysfunction is associated with increased oxidative stress and inflammatory reaction that contribute to coronary plaque instability and acute coronary events (22, 23). Lower serum adropin level was found in patients with acute MI than patients with stable angina pectoris or controls (9). Wu et al. (24) showed that serum adropin level was significantly associated with severity of CAD in patients with DM. Zhao et al. (25) revealed that low serum adropin level was associated with hyperhomocysteinemia and more severe coronary atherosclerosis, as reflected by higher SYNTAX score. Demirçelik et al. (10) revealed that adropin level is lower in patients with late saphenous vein graft occlusion and these reduced adropin levels . These studies suggested that adropin might have role on progression of atherosclerosis. Similarly, present study revealed that adropin level is lower in high SYNTAX (≥32) group than both low-moderate SYNTAX (<32) group and NCA group.

Adropin has role in hypertension via endothelial dysfunction. Aydın et al. (26) revealed that adropin is independent predictor of essential hypertension. Lian et al. (27) found that adropin has positive correlation with plasma level of brain natriuretic peptide, and these data suggested that elevated serum adropin level may have a role in the pathogenesis of heart failure.

Study limitations

The present study is a cross-sectional study with relatively small sample size. We did not measure adropin level after discharge and do not have follow up MACE data. Therefore, our results should be verified in multi-center prospective longitudinal studies with larger sample size. The limitations of this study should be considered when interpreting the results.

Conclusion

In conclusion, results of this study showed that serum adropin level was lower in the high SYNTAX group than low SYNTAX group in patients with NSTEMI. Adropin could have role in pathogenesis of atherosclerotic burden in patients with NSTEMI.

Conflict of interest: None declared.

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