RESEARCH ARTICLE / *Araştırma Makalesi*

An Analysis on Coronary Artery Disease Severity with Serum Adropin Level in Patients with Acute ST-Segment Elevation Myocardial Infarction

ST Segment Yükselmeli Miyokard İnfarktüsü Hastalarında Koroner Arter Hastalığının Ciddiyeti ile Serum Adropin Seviyesi Arasındaki İlişkinin Değerlendirilmesi

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Abstract

Objective	Adropin is associated with energy balance in tissues and organs. The SYNTAX score (SS) is used to determine the severity of ST-segment elevation myocardial infarction (STEMI). The aim of this study was to determine the relationship between serum adropin levels and disease severity in STEMI patients.
Materials and Methods	Eighty-nine patients who underwent coronary angiography (CAG) for STEMI were included in the study. The STEMI patients were divided into two subgroups: Group 1(SS < 22) and Group 2 (SS ≥ 23). 43 patients who underwent CAG and had normal coronary arteries were included in the study as a control group.
Results	Groups 1 and 2 included more male participants than the control group (89.7% and 74.2% vs. 34.9%, respectively, p < 0.001). The smoking rate was higher in Groups 1 and 2 than in the control group (55.1% and 34.4% vs. 11.6%, respectively, p≤0.001). Serum adropin levels were lower in Group 1 than in the control group (147.3 ± 149.2 mg/L and 228.1 ± 253.3 ng/L, p = 0.03). Serum adropin levels were the lowest in Group 2 (87.8 ± 23.2 ng/L, 147.3 ± 149.2 ng/L, and 228.1 ± 253.3 ng/L, p = 0.004). Serum adropin levels were also negatively correlated with SS (r = -0.33, p = 0.002).
Conclusion	Serum adropin levels decreased more in STEMI patients than in those without coronary artery disease (CAD). In addition, serum adropin levels decreased with increasing SS;this indicates the severity of CAD.
Keywords	Adropin; ST-segment elevation myocardial infarction; SYNTAX score

Öz

Amaç	*Adropin doku ve organların enerji balansı ile ilişkilidir. SYNTAX skor (SS) ST segment yükselmeli miyokard infraktüsünün (STYMI) ciddiyetinin değerlendirilmesinde kullanılmaktadır. Bu çalışmada serum adropinseviyesiile STYMI hastalarının hastalık ciddiyeti arasındaki ilişkinin araştırılması amaçlandı.*
Gereç ve Yöntemler	*STYMI sebebiyle koroner anjiografi (KAG) yapılan 89 hasta çalışmaya dahil edildi. STYMI hastalar Grup 1 (SS < 22) ve Grup 2 (SS ≥ 23) alt gruplarına ayrıldı. KAG yapılan ve normal koroner arterler izlenen 43 hasta ise control grubu olarak çalışmaya dahil edildi.*
Bulgular	*Grup 1 ve 2 de erkek cinsiyet control grubuna gore daha fazlaydı (sırasıyla % 89,7, 74,2 ve 34,9, p < 0.001). Sigara kullanım oranı Grup 1 ve 2 de kontrol grubuna gore daha fazlaydı (sırasıyla %55,1, 34,4ve 11,6, p≤0.001). Serum adropin seviyesi Grup 1 de kontrol grubuna göre anlamlı daha azdı (147,3 ± 149,2 mg/L ile 228,1 ± 253,3 ng/L, p = 0.03). Serum adropin seviyesi en düşük Grup 2 de saptandı (87,8 ± 23,2 ng/L, 147,3 ± 149,2 ng/L ve 228,1 ± 253,3 ng/L, p = 0.004). Serum adropin seviyesi SS ile negatif koroleydi (r = -0.33, p = 0.002).*
Sonuç	*STYMI hastalarında serum adropin seviyeleri koroner arter hastalığı (KAH) olmayanlara göre düşüktür. SS yükseldikçe serum adropin seviyeleri azalmaktadır, bu da KAH ciddiyetini göstermektedir.*
Anahtar Kelimeler	*Adropin; ST-segment yükselmeli miyokardial enfarktüs; SYNTAX skor*

INTRODUCTION

Clinical diagnosis of acute myocardial infarction (AMI), ischemic injury in the myocardium should be confirmed by cardiac biomarkers.[1] These biomarkers are not only used for diagnosis. They can also provide information about the extent of the infarct area within the affected area as well as the short-term and long-term prognose of the patient.[2] Biomarkers that can provide this information in cases of acute ST-segment elevation myocardial infarction (STEMI) are generally classified as enzymatic or non-enzymatic. The most well-known types of these biomarkers are enzymatic markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), and troponins.[3,4] These markers have advantages and disadvantages in AMI diagnosis. Currently, researches are ongoing to find novel biomarkers that can be used in both diagnosis and detection of disease extensiveness.

Adropin is a peptide that has initially been shown to be secreted from the liver and is known to be encoded by the energy homeostasis-associated (Enho) gene.[5] This peptide is associated with energy balance in tissues and organs. A decrease in serum adropin level may indicate an impairment of energy homeostasis in the myocardium.[6] Serum adropin levels decrease in many cardiovascular diseases including heart failure, AMI, and coronary atherosclerosis.[7-9] The syntax score (SS) is used to score the anatomical severity of coronary artery disease (CAD).[10] A high SS is a predictor of increased mortality and morbidity.[11] As the severity of CAD increases, the energy metabolism of the myocardium may further deteriorate and serum adropin levels may decrease. This hypothesis was confirmed by demonstrating that serum adropin levels decreased in myocardial infarction without ST elevation (NSTEMI) as the anatomical severity of CAD (SS ≥ 32) increased.[12] It was also recently shown that patients with AMI (with or without ST-segment elevation) and stable ischemic heart disease have lower adropin concentrations.[7]

The aim of the present study was to determine the relationship between serum adropin level, an indicator of myocardial energy metabolism, and CAD disease severity in acute STEMI patients.

MATERIALS and METHODS

This descriptive cross-sectional study was approved by Erzurum Education and Research Hospital Ethiccommittee (Approved number: 2018/18-184 and date:19.11.2018), all participants provided informed consent. A total of 482 patients who underwent coronary angiography (CAG) for STEMI in the Erzurum Education and Research Hospital between January 2019 and August 2019 were evaluated for the study. Patients with history of previous coronary artery bypass grafting (31 patients), known CAD (266 patients) and chronic kidney disease (46 patients), severe hepatic (8 patients) or renal dysfunction (22 patients), chronic inflammatory disease (3 patients), acute infection (11 patients), or malignancy (6 patients) were excluded from the study. Eighty-nine patients were included in the study. The control group was selected from a set of patients with normal coronary arteries as detected by CAG. The electrocardiographic criteria for STEMI were based on the Fourth Universal Myocardial Infarction Guide (2018). Patients were categorized as STEMI patients according to the following four criteria specified in this guide: 1. new ST-segment elevation at point J, greater than 1 mm in all two adjacent leads except V2 or V3; 2. in V2–V3, greater than 2 mm in men older than 40 years, greater than 2.5 mm in men younger than 40 years, or greater than 1.5 mm in women; 3. a newly developed left bundle branch block (patients with pre-existing left bundle branch blocks were further evaluated using the Sgarbossa criteria); and 4. ST-segment elevation in AVR (> 1 mm) combined with the absence of ST elevation in precordial leads; long, prominent, and symmetrical T waves in precordial leads; and a >1 mm upsloping-style ST-segment depression at point J in precordial leads.[1]

CAG was performed using the Judkins technique via the

femoral or radial artery according to the operator's preference. Images of each coronary artery were shown in at least two different planes. The SS was calculated separately for each patient by two experienced interventional cardiologists. If a difference of more than three was detected between the scores, a third cardiologist was consulted. The patient was excluded from the study if the dispute persisted. The SS was calculated using the calculator on the original website (www.syntaxscore.com). The STEMI patients were divided into two subgroups: Group 1(SS <22) and Group 2 (SS ≥23).

Laboratory Measurements

Blood samples were taken from the antecubital vein and centrifuged immediately to be used for adropin measurement just before CAG in patients with STEMI. Serum samples were stored at -80 °C until the day of analysis. The blood samples of the control group were taken from the antecubital vein and centrifuged immediately after CAG, and serum samples were stored at -80 °C until the day of analysis. Other biochemical parameters were studied using the samples obtained from the peripheral venous vessels at the time of admission to the emergency department. Serum adropin measurement was performed using the human adropin enzyme-linked immunosorbent method according to the manufacturer's protocol (Commercial kit name: Human Adropin ELISA kit, catalog no: E3231 Hu, unit: ng/L, limit range: 5–1000 ng/L; Bioassay Technology Laboratory, Shanghai, China).

RESULTS

The baseline demographic characteristics of the patient groups are shown in Table 1. Groups 1 and 2 had more male patients thanthe control group (89.7% and 74.2%vs. 34.9%, respectively, p< 0.001). The rates of hypertension, diabetes mellitus, and hyperlipidemia were similar between the groups. The smoking rate was higher in Groups 1 and 2 than in the control group (55.1% and 34.4%vs. 11.6%, respectively,p ≤ 0.001). Rates of antihypertensive, statin, insulin, and oral antidiabetic drug use were similar in both groups. The mean amount of time from the onset of chest pain to the diagnosis of STEMI was 4.8 ± 3.4 hours. Thirty-two (35.9%) of the patients had anterior myocardial infarction, 51 (57.3%) had inferior myocardial infarction, and 6(6.8%) had other side myocardial infarction.

The laboratory characteristics of the patient groups are shown in Table 2. The mean SS of the STEMI patients was 19.2 ± 10.9; 60 (67.4%) patients had scores below 22 (Group 1), and 29 (32.6%) patients had scores of 23

Table 1. Baseline clinical characteristics of the STEMI and normal coronary artery patients

Variables	Group 1 (n=58)	Group 2 (n=29)	Control (n=43)	p value
Age (years)	58.8±11.1	63.5±14.1	59.9±9.1	0.187
Male gender, n (%)	52 (89.7)	21 (72.4)	15 (34.9)	**<0.001**
BMI(kg/m2)	24.96±3.84	25.53±4.01	25.26±3.32	0.761
HT, n (%)	22 (37.9)	14 (48.2)	22 (41.5)	0.155
DM, n (%)	16 (27.5)	12 (41.3)	13 (30.2)	0.513
HPL, n (%)	10 (17.2)	5 (17.2)	8 (18.6)	0.269
Smoking status, n (%)	32 (55.1)	10 (34.4)	5 (11.6)	**<0.001**
ACE inh./ARB, n (%)	20 (34.4)	11 (37.9)	20 (46.5)	0.248
Statin, n (%)	4 (6.8)	3 (10.3)	2 (4.6)	0.458
OAD, n (%)	14 (24.1)	8 (27.5)	10 (23.2)	0.865

Data are presented as mean ± standard deviation and median (first quartile-third quartile).
Abbrevations: ACE: angiotensin converting enzyme, ARB: angiotensinogen receptor blockers,BMI: body mass index, OAD: oral antidiabetics,DM: diabetes mellitus, HPL: hyperlipidemia, HT: hypertension,STEMI: ST-Segment Elevation Myocardial Infarction

Table 2. Laboratory and angiographic variables among STEMI and normal coronary artery patients				
Variables	**Group 1 (n=58)**	**Group 2 (n=29)**	**Control (n=43)**	**p value**
Glucose, mg/dl	150.9±72.9	171.6±110.5	135.4±63.5	0.107
Creatinine, mg/dl	0.97±0.28	1.01±0.29	0.93±0.14	0.092
Total cholesterol, mg/dl	204 (179.5-232)	192 (171.8-224.5)	181 (155.3-232.8)	0.285
Triglycerides, mg/dl	174.3±124.6	163.9±108.6	180.7±84.6	0.216
LDL, mg/dl	137.5 (109-158)	127 (109-153)	118.5 (97.5-142.5)	0.112
HDL, mg/dl	39.9±8.4	43.6±16.3	40.4±12.7	0.398
AST, mg/dl	65.6±95.8	69.8±68.9	22.4±7.1*‡	**0.005**
Hemoglobin, g/dl	15.2 (14.1-16.4)	14.6 (13.2-15.7)	14.6 (13.5-15.7)	0.175
WBC x103 mm2	12±3.7	12.1±2.9	8.1±1.6*‡	**<0.001**
Platelet x103 mm2	247 (196-301.8)	227 (190.5-312.5)	266 (232.8-306.3)	0.199
Adropin, ng/L	147.3±149.2	87.8±23.2*	228.1±253.3*‡	**0.004**

Data are presented as mean ± standard deviation and median (first quartile-third quartile). The symbol * indicates the difference from Group 1 and the symbol ‡ indicates the difference from Group 2.
Abbrevations:AST:aspartate aminotransferase,HDL: high density lipoprotein, LDL: low density lipoprotein,STEMI: ST-Segment Elevation Myocardial Infarction,WBC: white blood cell count,

or above (Group 2). Groups 1 and 2 had similar blood cholesterol, glucose, creatinine, and hemoglobin levels to those of the control group. Groups 1 and 2 had higher AST levels (65.6 ± 95.8 mg/dl and 69.8 ± 68.9 mg/dl vs. 22.4 ± 7.1 mg/dl, respectively, p = 0.001) and white blood cell counts (12 ± 3.7mm2and 12.1 ± 2.9 mm2vs. 8.1 ± 1.6 x103 mm2, p<0.001) than the control group. Serum adropin levels were significantly different between the groups (87.8 ± 23.2 ng/L, 147.3 ± 149.2 ng/L, and 228.1 ± 253.3 ng/L, p = 0.004), and a post-hoc analysis showed a significant difference between the mean serum adropin level of Group 1 and that of the control group (147.3±149.2 ng/L and 228.1±253.3 ng/L, p=0.03). A significant difference was also found between the serum adropin levels of Groups 1 and 2 (87.8 ± 23.2 ng/L vs. 147.3 ± 149.2 ng/L, p = 0.017). Serum adropin levels were negatively correlated with SS (r = -0.33, p = 0.002; Figure 1).

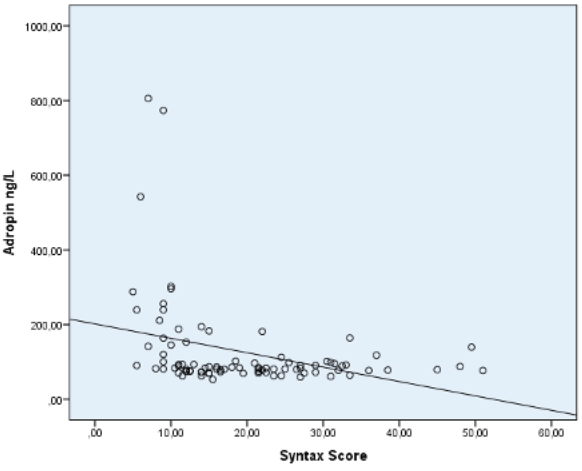

Figure 1.Relationship between serum adropin level and syntax score

DISCUSSION

In the present study, serum adropin levels, indicating energy homeostasis of the myocardium, were found to be significantly lower in STEMI patients than in patients without CAD. This biomarker was negatively correlated with SS, indicating the severity of CAD in the STEMI patient group.

Studies of diabetic mice have revealed that adropin, a peptide known to be encoded by the Enhogene,is expressed in the pancreas, cerebellum, kidney, and heart (endocardium, pericardium, and myocardium).[13] Adropin is thought to have effects on energy hemostasis, lipid metabolism, and insulin response.[5,14] In particular, the effects of adropin on glucose and lipid homeostasis may play a role in the development of arteriosclerosis. It has previously been shown that serum adropin levels decrease in CAD9. Endothelial dysfunction, oxidative stress, and inflammatory reaction all play roles in the destabilization of coronary artery plaque.[15,16] Adropin is known to have protective effects on endothelial functions.[17] In addition, adropin has been found to have antioxidant properties.[18] Decreased adropin levels can lead to deterioration of both endothelial functions and myocardial energy homeostasis. Low serum adropin levels in cases of CAD reflect high SS and are associated with more severe coronary atherosclerosis.[19] The results of the present study support the body of literature that has evidenced the relation between increasing SS and decreasing serum adropin levels in STEMI patients.

The SS calculated before percutaneous coronary intervention in STEMI patients is an important predictor of long-term mortality.[12] This prognostic parameter is used to rate the anatomical severity of CAD10, but it does not provide any information concerning the energy homeostasis of the myocardium. As the severity of CAD increases, the energy homeostasis of the myocardium may deteriorate. The present study is the first in the literature to demonstrate that this hypothesis is acceptable in isolated STEMI patients. It has previously been shown that serum adropin levels were lower in AMI (without separating STEMI and non-STEMI) groups than in stable angina pectoris and healthy control groups.[7] However, no classification was performed for myocardial infarction types in this study. The present study focused on isolated STEMI patients. A previous study has shown that serum adropin levels decrease as SS (indicating CAD severity) increases in non-STEMI patients20. In the present study, a negative correlation was found between SS and serum adropin levels; this finding was similar to the results concerning non-STEMI patients.

Limitations

This study was designed as a prospective cross-sectional study, and major adverse cardiac events were not investigated. As a potential prognostic biomarker, we were unable to determine the effect of the relationship between serum adropin levels and decreased myocardial homeostasis with increasing SS on clinical endpoints in STEMI patients.

CONCLUSION

Serum adropin levels decreased more in STEMI patients than in patients without CAD. In addition, serum adropin levels decreased as SS increased. Myocardial homeostasis may deterioratefurther as the severity of CAD increases in STEMI patients.

Declaration of Conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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