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The assessment of plasma asprosin levels in acute coronary artery disease and its correlation with HEART score

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Abstract

Objective: It was aimed to compare the serum asprosin levels in patients with ischemic heart disease with healthy subjects, and to evaluate the relationship between asprosin levels with HEART score and mortality in the patients with coronary heart disease.

Material and methods: This study was designed as a single-center, prospective study. Sixty-two patients who presented with acute chest pain and underwent digital subtraction coronary angiography and 31 healthy subjects were included in the study. Fasting serum asprosin levels were compared between patients and healthy individuals. The HEART score was calculated for each individual, and its relations with asprosin and one-month mortality were evaluated.

Results: The minimum age of 93 cases included in the study was 24, the maximum age was 85, and the median age was 64. HEART score was higher in cases who had mortality within one month ($p<0.0001$). Plasma asprosin values were higher in patients with one-month mortality ($p<0.0001$) and lower in the control group compared to the study group ($p=0.015$). There is a statistically significant weak positive correlation between HEART score and asprosin value ($p=0.006$, $r=0.285$).

Conclusion: Serum asprosin level can be used both diagnostically and as a biochemical marker in the evaluation of mortality and prognosis in patients with ischemic heart disease.

Key words: acute chest pain, asprosin, HEART score

Introduction

Asprosin is a newly defined centrally acting orexigenic adipokine secreted from white adipose tissue that regulates glucose metabolism [1]. Increased asprosin levels are shown in patients with clinical conditions associated with metabolic syndrome such as obesity, coronary artery disease, insulin resistance, polycystic ovarian disease, lipid metabolism, anaerobic and aerobic exercise, type 1 and type 2 diabetes mellitus, and non-alcoholic fatty liver disease [2-4]. It is known that blood asprosin level has a positive correlation with body mass index [5]. Besides, significant changes were found in plasma asprosin levels in patients with anorexia nervosa, anorexic cachexia in cancer patients and malignant mesothelioma [6].

There are very few studies in the literature evaluating heart diseases and serum asprosin levels, and current studies suggest that asprosin has a protective effect on myocardial cells and is associated with ischemic heart diseases [7]. The relationship between acute coronary syndrome and asprosin has not been clearly elucidated yet. It is also not defined the relationship between plasma asprosin level and the prognosis of the disease in these cases. The correlation of asprosin with the HEART

scoring, used in the prognosis of the disease in triage as an essential cornerstone in the diagnostic-therapeutic decision, is not investigated. It is thought that the asprosin level may be a diagnostic and prognostically significant marker in this sense.

In this study, it was aimed to compare the plasma asprosin levels in patients with the acute coronary syndrome with healthy individuals in similar age groups and examine the relationship between the HEART score and plasma asprosin level at the time of admission in patients with ischemic heart disease to aid physicians in making a timely appropriate management of patients.

Material and methods

Study design and setting

This study was designed as a single-center, prospective study. The results are reported in accordance with Standards for Reporting of Diagnostic Accuracy Studies (STARDS). Before the study, the local ethics committee approval (23.01.2020 date and 2020/1-3 number) was obtained, and the research was conducted between 01.02.2020-01.05.2020 afterward. Before the study, an informed consent form was obtained from all included cases.

Selection of participants

The study group consisted of 62 cases who a presented to the emergency department with acute chest pain and underwent digital subtraction coronary angiography between 01.02.2020-01.05.2020 and 31 cases without known heart or metabolic disease constituted the control group. Subjects under 18 years of age and those who refused to give informed consent were excluded from the study. Cases with obesity (body mass index >30), polycystic ovarian disease, omission - anoxia nervosa, heart disease, type 1 or type 2 diabetes, and patients who exercised heavily in the last six hours were not included in the control group.

Interventions

In order to determine the asprosin level, blood samples were obtained from venous blood between 7-9 am after overnight fast both study group and the control group. The samples were collected in EDTA tubes, and after 15 minutes of centrifugation at 1500 rpm, the plasma was obtained. The plasma samples obtained were stored at -860. ELISA kit (Sunred Biological Technology Cooperation, Shanghai, China) with high sensitivity to human asprosin level (<0.938 ng/ml) was used to determine plasma asprosin concentration. The manufacturer's instructions were followed in the measurement.

Measurements

Demographic data including age and gender were analyzed. One month mortality, treatment methods and involved coronary arteries in coronary artery disease were recorded. Artery stenosis were group as LAD and the other arteries.

HEART scoring was made according to the patients' evaluation in the study group at the time of admission to the emergency department in accordance with the scoring system specified in the literature, the patient's history, ECG, risk factors of the patients for coronary artery disease and the troponin level at the time of admission were recorded [3,4]. HEART scores between 0 and 10 were obtained by giving 0, 1, or 2 points for each item. Information showing the detailed evaluation of scoring is shown in Table 1.

Table 1 HEART scoring system applied in the study

History	• High suspicion • Moderate suspicion • No or slight suspicion	• 2 points • 1 point • 0 points
ECG	• Significant ST-Depression • Nonspecific Repolarization • Normal ECG findings	• 2 points • 1 point • 0 points
Age	• ≥ 65 years • Between 45-65 years • ≤ 45 years	• 2 points • 1 point • 0 points
Risk Factors	• ≥3 risk factors or history of coronary artery disease • 1 or 2 risk factors • No risk factors	• 2 points • 1 point • 0 points
Troponin • • • •	• ≥3 x Normal limit • Abnormal troponin but <3x upper limit • Normal troponin	• 2 points • 1 point • 0 points
Risk factors: Diabetes Mellitus, current or recent smoker, hypertension, hyperlipidemia, family history of coronary artery disease, obesity		

Outcomes

A comparison of asprosin levels between the study group and the control group constitutes the primary outcome. The correlation between the HEART scoring obtained from the patients in the study group and the asprosin levels represents the secondary outcome. Other secondary outcomes are the comparison of age and gender between the study group and the control group, the relationship of serum asprosin level with mortality, treatment methods presented at the time of admission, findings obtained after angiography in the patients in the study group.

Analysis

SPSS 21.0 (SPSS Inc., Chicago, IL) software was used for statistical analysis. Categorical data are expressed in numbers and percentages. Pearson's chi-square and Fisher's exact tests were used to compare categorical data with each other. Shapiro Wilk test was used to evaluate the distribution pattern of numerical data. Since numerical data do not show a normal distribution, Mann Whitney-U and Kruskal Wallis tests were used to compare numerical data with categorical data. In cases where a significant relationship was found in the group comparisons, the sensitivity and specificity values were calculated with the ROC analysis at the most appropriate cut-off values. Spearman correlation analysis was used to compare the numbers and data with each other. Statistical analyzes where the p-value is less than 0.05 was considered to be significant.

Results

Characteristics of study subjects

Of the 93 cases included in the study, 62 were the study group (66.7%), and 31 were the control group (33.3%). 41 (44.1%) of the cases were male, and 52 (55.9%) were female. The minimum age of 93 cases included in the study was 24, the maximum age was 85, and the median age was 64.

Mortality was observed within a month in 10 (16.1%) of the cases constituting the study group. In the classification made according to treatment methods, percutaneous coronary angiography was performed in 52 cases, and stent or balloon treatment was arranged. Coronary artery by-pass grafting was performed in 3 cases (4.8%) after coronary angiography. In 7 cases (11.3%), the interventional therapeutic procedure was not

presented during or after coronary angiography. In the evaluation of coronary angiographies of the patients in the study group, left descending artery stenosis was found in 11 cases (17.7%), while circumflex artery stenosis was found in two cases (3.2%). No stenosis was found in the coronary arteries in 44 cases (71%). In 5 cases (8.1%), stenosis was observed in more than one coronary artery.

According to the classification made according to the blood troponin value in the study group, troponin value at presentation was high (>0.4 ng / mL) in 18 cases (29%), while it was within normal limits in 44 cases (71%). In the evaluation made according to the HEART score, the minimum HEART score was 1, the maximum HEART score was 10, and the median HEART score was 4.5.

Main Results

There is no statistically significant relationship between sex and plasma asprosin level, between gender and HEART score, and sex and troponin level (p=0.951, 0.173, and 0.937, respectively). There was no statistically significant difference in age between the study group and the control group (p=0.18) (Table 2).

Table 2 Characteristics of study and control groups

	Study group	Control group	p-value
Age (median, min-max)	64 (24-85)	55 (35-77)	0.07
Male (n, %)	31 (50%)	10 (24.4%)	0.104
HEART score (median, min-max)	4.5 (1-10)	0	<0.0001*
Asprosin, ng/mL (median, min-max)	119.6 (77.8-388.6)	102.2 (78.9-280.1)	0.015*
Troponin ng/mL (median, min-max)	0 (0-13)	-	-

A statistically significant difference was found in the comparison of the HEART score between the study group and the control group, and the HEART score in the study group was statistically higher (p<0.0001). A statistically significant difference was also observed in the comparison of asprosin values between the study group and the control group (p=0.015). Parameters of the study group and their comparison between the survivor and non-survivor groups are given in Table 3.

Table 3 Parameters of the study group and their comparison between the survivor and non-survivor groups

	Non- survivor	Survivor	p-value
Age (median, min-max)	75 (33-84)	64 (24-85)	0.246
HEART score (median, min-max)	9.5 (8-10)	4 (1-9)	<0.0001*
Asprosin, ng/mL (median, min-max)	288.8 (92.7-388.6)	112.7 (77.8-196.4)	<0.0001*
Troponin, ng/mL (median, min-max)	0.053 (0-13)	0 (0-3.5)	0.058

The one-month mortality rate for the male of the study group was 22.6% and for female 9.7%. The difference in mortality rate in the working group by gender was not statistically significant (p=0.167). When mortality was compared with age, no statistically significant relationship was found between the mean age of the cases with one-month mortality (p=0.246).

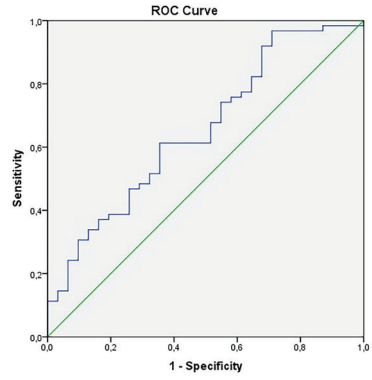
There was no statistically significant relationship between troponin and asprosin levels (p=0.828). When one-month mortality and troponin level was compared, one-month mortality was present in 5 (27.8%) of 18 cases with high troponin value, while one-month mortality was present in 5 (11.4%) of 44 cases with normal troponin value. The relationship between them is not statistically significant (p=0.137). While normal findings were obtained in 9 (50%) of 18 cases with high troponin value, normal angiography findings were found in 35 (79.5%) of 44 cases with normal troponin value (p=0.033).

In the comparison between mortality and HEART score, the HEART score was higher in cases with one-month mortality (p<0.0001). In the comparison of mortality and asprosin value, a statistically significant relationship was found, and the asprosin value was statistically higher in cases with mortality within one month (p<0.0001). When comparing the troponin value between the survivor and non-survivor groups the p-value was found to be 0.058, and a significant relationship was not obtained. Numerical data showing the relationship between mortality and numerical data are detailed in Table 3.

In the comparison between the HEART score and the coronary angiography findings of the patients in the study group, a statistically significant relationship was found (p<0.0001). In paired group comparisons, a statistically significant difference was found between cases with normal coronary angiography findings and cases with more than one coronary artery stenosis, and the HEART score was found to be lower in cases with normal findings on angiography (p=0.005). In addition, a statistically significant difference was found between the HEART score of patients with normal coronary angiography findings and patients with LAD stenosis, and the HEART score was higher in cases with LAD stenosis (p<0.0001). No statistically significant difference was found in the artery stenosis groups (p>0.05).

A statistically significant result was obtained in the ROC analysis to determine the relationship between asprosin and coronary artery disease (p=0.015). The area under the curve was calculated as 65.6%, sensitivity 61.3%, specificity 64.5% at a cut-off value of 109.5 ng/mL (Figure 1).

Figure 1 - ROC curve in the comparison of plasma asprosin level between study and control groups



A statistically significant (p<0.0001) relationship was found in the ROC analysis performed to evaluate the relationship between asprosin and mortality, and the area under curve was calculated as 92.1%. 90% sensitivity and 100% specificity values were obtained at the cut-off value of 236.55 ng/mL (Figure 2).

A statistically significant correlation was found in the ROC analysis between the HEART score and mortality (p<0.0001), and the area under curve was calculated as 98.3%. When the cut-off value was 7.5, the sensitivity was 100%, and the specificity was 92.3% (Figure 2).

Figure 2 - ROC curve in the relationship between plasma asprosin level (first), HEART score (second) and one-month mortality

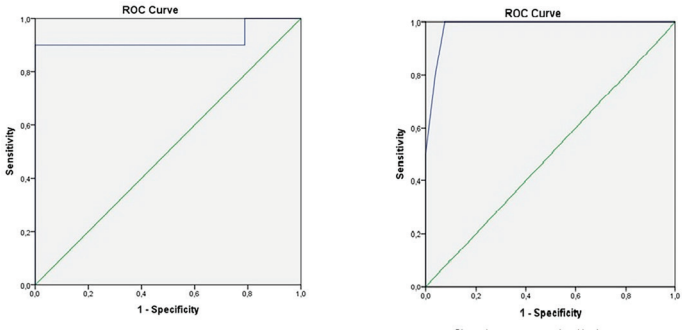
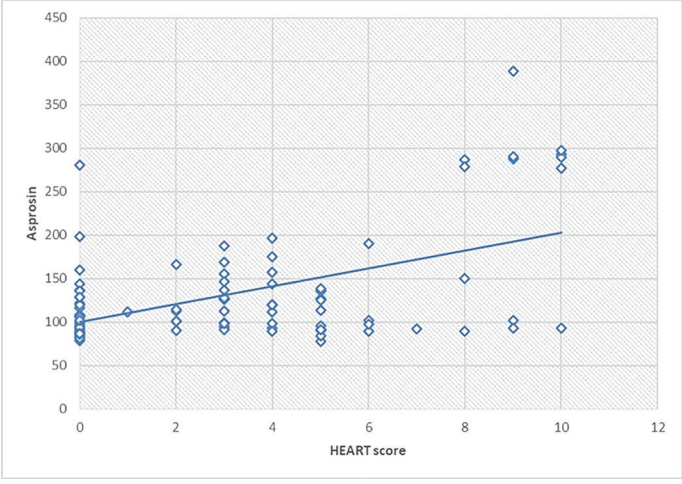


Figure 3 - Scattered plot graphic demonstration correlation between plasma asprosin level and HEART score



In correlation analysis, a statistically significant weak positive correlation was found between age and HEART score (p=0.03, r=0.309). There was no statistically significant correlation between age and asprosin and troponin values (p=0.182 and 0.128). There was a statistically significant weak positive correlation between the HEART score and the plasma asprosin level (p=0.006, r=0.285) (Figure 3). A statistically significant moderate positive correlation was found in the comparison of HEART score and troponin values (p<0.0001, r=0.583). There was no significant correlation when comparing asprosin and troponin values (p=0.966).

Discussion

Asprosin, a protein adipokine discovered in recent years, increases glucose release by activating the G protein-cAMP-PKA pathway in the liver [8]. Asprosin is the C-terminal product of the fibrillin protein encoded by the FBN1 gene, crosses the blood-brain barrier, and activates the hypothalamic circulation and affects adiposity by increasing appetite [9]. In this study, the relationship of this hormone, which is known to be associated with glucose metabolism and metabolic syndrome, with coronary artery disease was evaluated. Asprosin was found to be higher in patients with coronary artery disease than in healthy individuals. Moreover, it was concluded that patients with higher HEART score in coronary artery disease have higher asprosin levels. In addition, blood asprosin level was found to have high sensitivity (90%) and specificity (100%) in determining mortality within one month.

Although there are no studies in the literature that directly examine the relationship of serum asprosin level with HEART scoring and ischemic heart disease mortality, there are several studies evaluating asprosin associated with coronary heart disease. In a study, it has been shown that asprosin has a protective effect from apoptosis caused by the presentation of hydrogen peroxide in myocardial cells [10].

In another study, asprosin levels were compared with SYNTAX scoring used in ischemic heart disease. As a result, a significant positive correlation was obtained between serum asprosin level and SYNTAX score. This suggests that asprosin may show the severity of acute coronary syndrome in unstable angina pectoris cases and that asprosin may play a predictive role in cardiovascular diseases [11,12]. Unlike HEART scoring, SYNTAX scoring is based only on imaging findings in coronary angiography and does not include clinical and laboratory findings [13]. It is not a scoring system used in triage like HEART scoring. Nevertheless, it can be said that parallel results were obtained with this study since this study also showed the relationship between coronary artery disease findings in the coronary system and serum asprosin level. Besides, in this study, when the HEART score and coronary angiography findings were compared, it was found that the patients with stenosis in two or more coronary arteries also had higher HEART scores.

In a meta-analysis conducted in 2018, 25 studies between 2010 and 2017 were evaluated, and data on 25266 cases were collected. According to the results of the study, it has been shown that patients' HEART score can predict major cardiac events in the short term with high sensitivity, high negative predictive value and likelihood ratio [14]. Similarly, in this study, it was shown that one-month mortality was higher in cases with high HEART scores. Eight or more HEART scores were found to have high diagnostic value with 100% sensitivity and 92.3% specificity at one- month mortality prediction.

In the current literature, the number of scientific studies examining the relationship of asprosin with ischemic heart disease is limited. There are no studies in the current literature examining the HEART score and asprosin level and comparing the serum asprosin level with the mortality rate. This study provides preliminary and illuminating data that asprosin is higher in the non-survivors and study groups and shows that the value of asprosin can be used to predict short-term mortality in patients with ischemic heart disease. On the other hand, the lack of correlation between asprosin level and troponin level may indicate that asprosin provides additional information as a marker independent of the troponin level.

In retrospect, in addition to the asprosin level at presentation, evaluation of the asprosin level at follow-up in patients who responded to treatment, compared to other cases, could have yielded more impressive results for this study. In addition, it is remarkable that asprosin hormone, whose protective effect on the myocardium has been shown in the literature, is associated with mortality in metabolic syndrome and coronary artery disease, so the comparison of asprosin levels between coronary artery disease cases with and without metabolic syndrome and its relationship with mortality in these cases could provide additional valuable information.

Limitations

There are some limitations to this study. First, the fact that the study is single-centered and the number of cases in the study and control groups are limited are among the factors that may affect the result of the study.

Second, in this study, a single commercial kit was used to evaluate the asprosin level in plasma. In the publications mentioned in the literature, it is seen that various trademarks kits

are used in asprosin measurements. This may affect the study results.

Thirdly, one month was used as the limit in the evaluation of mortality, and statistical analysis was not performed in this sense, as specific mortality time was not recorded. The time of mortality could not be compared with the asprosin level.

Fourth, the total number of your patients is insufficient for proper ROC analysis (there must be 100 and higher in each sample). It appears to be extremely difficult to get statistically significant p-values in fewer cases. However, we presented the p values we found because they were statistically significant. So, ROC analysis results may need to be validated with large samples.

Fifth and last, only the patients who presented to the emergency department during the study and had coronary angiography constituted the study group. Coronary artery disease may result in sudden cardiac death, or there may be cases with coronary artery disease for which coronary angiography is not planned in the first line assessment. In this respect, the patients in the study group may not reflect the general profile of acute coronary artery disease.

In summary, according to the results of our study, serum asprosin level and HEART score have high sensitivity and specificity in predicting mortality in coronary artery disease. There is a significant correlation of asprosin level with HEART scoring. Asprosin levels are higher in patients with ischemic heart disease than healthy individuals. Serum asprosin level can be used as a biochemical marker in the evaluation of mortality and prognosis in patients with ischemic heart disease. Given the possible role of confounding factors, we recommend confirming our results with further larger cohorts, multicenter studies.

Ethical Considerations: Ethical approval for this study was obtained from Adıyaman Training and Research Hospital Ethics Committee. (23.01.2020 date and 2020/1-3 number) The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

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