ORIGINAL ARTICLE

Fibulin-1 and fibulin-5 as rule-out tests for non–ST-elevation myocardial infarction in the emergency setting

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KEY WORDS
fibulin, non–ST-segment elevation myocardial infarction, rule-out test

ABSTRACT

BACKGROUND Fibulin-1 and fibulin-5 are extracellular glycoproteins from the fibulin family. Both are expressed in the vessel wall and protect against vascular damage.

AIMS We aimed to investigate whether fibulin-1 and -5 may be used to exclude non–ST-segment elevation myocardial infarction (NSTEMI) in the emergency setting.

METHODS The study included 48 patients in the NSTEMI group and 42 controls who presented with chest pain of noncardiac origin as confirmed by a comprehensive evaluation including coronary angiography. Blood samples for fibulin-1, fibulin-5, and troponin I measurements were drawn on admission to the emergency department.

RESULTS Demographic characteristics were similar in patients with NSTEMI and controls. The median levels of both glycoproteins were lower in patients with NSTEMI as compared with controls: fibulin-1, 96.9 µg/ml (interquartile range [IQR], 20–503 µg/ml) vs 111.5 (IQR, 71–457 µg/ml), $P = 0.01$, and fibulin-5, 38 ng/ml (IQR, 15–509 ng/ml vs 57 ng/ml (IQR, 26–631 ng/ml), $P < 0.001$. The receiver operating characteristic curve analysis revealed the cutoff value of 105.6 µg/ml for fibulin-1 and of 49.4 ng/ml for fibulin-5 to exclude NSTEMI on admission.

CONCLUSIONS The present study demonstrated that fibulin-1 and -5 measurements might be used to exclude NSTEMI in patients admitted to the emergency department with acute chest pain.

INTRODUCTION Despite the substantial improvement in risk stratification, advancement in antiplatelet therapy, and the widespread use of invasive strategies, acute myocardial infarction still constitutes the major cause of morbidity and mortality worldwide and accounts for one-third of deaths in developed countries.[1] Non–ST-segment elevation myocardial infarction (NSTEMI) is a common type of myocardial infarction, which is characterized by the absence of ST-segment elevation on the surface electrocardiogram. Recent guidelines on non–ST-segment elevation acute coronary syndromes (ACSs) have recommended that early implementation of an invasive strategy within hours of presentation increases survival rate, particularly in patients with a high-risk profile on admission.[2] Therefore, among patients presenting with acute chest pain but without ST-segment elevation, identification of individuals with NSTEMI who are candidates for an early invasive treatment is critical to improve prognosis in this population. Adequate discrimination of patients with NSTEMI from those without ACS also spares patients with noncardiac chest pain unnecessary invasive procedures.

Fibulin-1 and fibulin-5 belong to the fibulin family of extracellular glycoproteins. Fibulin-1 is physiologically present in blood at high concentrations and is expressed in the vessel wall

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WHAT'S NEW?

Identifying patients who need early invasive treatment for non–ST-segment elevation myocardial infarction (NSTEMI) among those with acute chest pain and no ST-segment elevation is critical to improve prognosis in this population. Fibulin-1 and fibulin-5 belong to the fibulin family of extracellular glycoproteins. Fibulin-1 is expressed in the vessel wall and cardiac valves. In turn, fibulin-5 is expressed by endothelial cells. Both proteins were shown to exert protective effects against vascular damage. The present study demonstrated for the first time that fibulin-1 and -5 might be used as a rule-out test to exclude NSTEMI in patients with acute chest pain in the emergency setting.

and cardiac valves.[3] On the other hand, fibulin-5 has been shown to be expressed by endothelial cells. Both proteins were shown to exert protective effects against vascular damage.[4] However, data on the role of fibulin-1 and -5 in atherosclerotic vascular diseases, particularly in coronary artery disease, are lacking.

In this study, we compared the levels of fibulin-1 and -5 between patients with NSTEMI and those with noncardiac chest pain. In addition, we aimed to investigate whether these 2 extracellular glycoproteins have any role in excluding NSTEMI in the emergency setting.

METHODS **Patient selection** The present cross-sectional study included patients aged between 30 and 85 years admitted to the coronary care unit of Adnan Menderes University Hospital in Aydin, Turkey, with a diagnosis of NSTEMI between September 2017 and June 2018. Patients with chronic noncardiac diseases (malignancy, acute or chronic inflammatory diseases, renal or hepatic insufficiency, advanced chronic obstructive pulmonary disease, active infection), aortic aneurysm, previous cerebrovascular events, peripheral vascular disease, ejection fraction of less than 50%, and those with cardiogenic shock on admission were excluded. After applying the exclusion criteria, a total of 48 patients were enrolled in the NSTEMI group. Patients who presented to the emergency department with chest pain of noncardiac origin based on a comprehensive evaluation including coronary angiography (normal coronary arteries) were recruited as controls (n = 42). Routine laboratory tests as well as troponin measurement were performed on admission. For the purpose of this study, NSTEMI was defined as an increase in cardiac troponin I levels with at least one value above the 99th percentile of the upper reference limit in addition to symptoms or electrocardiographic, echocardiographic, and angiographic signs of ischemia.[6] All patients underwent transthoracic echocardiography to measure the ejection fraction before discharge.

Fibulin-1 and -5 measurements Blood samples for fibulin-1 and -5 measurements were drawn on admission. Within 30 minutes, samples were centrifuged at 5000 *g* for 6 minutes, and the resulting supernatants were stored at −80°C until analysis. Human FBLN1 and FBLN5 enzyme-linked immunosorbent assay kits (Abcam, Cambridge, Massachusetts, United States) were used to determine serum fibulin-1 and -5 levels. Following the measurements, all results were recorded in patients' charts.

Ethical approval All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Ethics Committee (AMUKAEK; June 8, 2017; No. 2017/1126), and written informed consent was obtained from all participants.

Statistical analysis Power calculations based on our pilot study with 20 patients revealed that at least 42 patients were required in each group for an adequate sample size (mean [SD] fibulin-1 levels, 101 [26 µg/ml] in the NSTEMI group and 126 [38 µg/ml] in the control group; effect size, 0.80; α error, 0.05; power, 0.8).[5] All statistical analyses were performed using the SPSS software v. 15.0 (SPPS, Chicago, Illinois, United States). Continuous variables were presented as means (SD), and categorical variables, as numbers and percentages. The Shapiro–Wilk test was used to determine the distribution of variables. Continuous variables were compared with the *t* test and Mann–Whitney test. Categorical variables were compared with the χ^2 test. To identify the predictive value of fibulin-1 and -5 for NSTEMI, a binary logistic regression analysis was used. Finally, the receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff values for fibulin-1 and -5 for differentiating between patients with noncardiac chest pain and those with NSTEMI. A 2-tailed *P* value of less than 0.05 was considered significant.

RESULTS The mean (SD) age of the study population was 60 (11) years. There were 60 men (66.7%) and 30 women (33.3%). Patients with NSTEMI did not differ from controls in terms of age, sex, prevalence of smoking, presence of diabetes and hypertension, body mass index, blood glucose, creatinine, and hemoglobin levels, as well as leukocyte and platelet count (TABLE 1). In patients with NSTEMI, the mean (SD) time from symptom onset to blood sampling was 116 (28) minutes. As expected, admission cardiac troponin I levels were higher in patients with NSTEMI than in controls (mean [SD], 3.84 [11.2] ng/ml vs 0.13 [0.01] ng/ml, *P* <0.001). However, the median levels of both glycoproteins were lower in patients with NSTEMI than in controls: fibulin-1, 96.9 µg/ml (IQR,

TABLE 1 Demographic data and laboratory results in patients with non–ST-segment elevation myocardial infarction and patients with chest pain of noncardiac origin (controls)

Parameter		NSTEMI (n = 48)	Controls (n = 42)	*P* value
Age, y, mean (SD)		61 (12)	59 (9)	0.37
Male sex, n (%)		32 (66)	28 (66)	1
Diabetes, n (%)		23 (48)	12 (28)	0.08
Hypertension, n (%)		23 (48)	15 (35)	0.29
Smoking, n (%)		18 (37)	9 (21)	0.11
BMI, kg/m^2, mean (SD)		30.3 (4.0)	28.9 (4.7)	0.18
Glucose, mg/dl, mean (SD)		124 (47)	110 (33)	0.11
Creatinine, mg/dl, mean (SD)		1.1 (0.8)	0.9 (0.2)	0.07
Hemoglobin, g/l, mean (SD)		12.5 (2.1)	12.2 (1.3)	0.49
Leukocytes, × 10^3/µl, mean (SD)		10.1 (3.2)	10.6 (1.8)	0.4
Platelets, × 10^3/mm^3, mean (SD)		251 (80)	258 (87)	0.67
Troponin I, ng/ml, median (IQR)		4.2 (0.8–9.6)	0.1 (0.04–0.22)	<0.001
Fibulin-1, µg/ml	Mean (SD)	118 (57)	153 (68)	0.001[a]
	Median (IQR)	96.9 (20–503)	111.5 (71–457)	
Fibulin-5, ng/ml	Mean (SD)	58 (37)	107 (65)	<0.001[a]
	Median (IQR)	38 (15–509)	57 (26–631)	

a Mann–Whitney test

SI conversion factors: to convert glucose to mmol/l, multiply by 0.0555; creatinine to µmol/l, by 88.4.

Abbreviations: BMI, body mass index; NSTEMI, non–ST-segment elevation myocardial infarction

TABLE 2 Predictive value of selected variables for the presence of non–ST-segment elevation myocardial infarction on logistic regression analysis

Parameter	Odds ratio	95% CI	*P* value
Fibulin-1 on admission	0.99	0.98–0.1	0.04
Fibulin-5 on admission	0.98	0.97–0.1	0.02
Presence of diabetes	4.3	1.06–17.48	0.04
Creatinine on admission	2.11	0.75–5.98	0.16

20–503 µg/ml) vs 111.5 µg/ml (IQR, 71–457 µg/ml), *P* = 0.01, and fibulin-5, 38 ng/ml (IQR, 15–509) vs 57 (IQR, 26-631 ng/ml), *P* <0.001. The in-hospital mortality rate was 9% for NSTEMI patients (n = 4), while no deaths occurred among controls (*P* = 0.06).

The logistic regression analysis revealed that, in addition to diabetes (odds ratio [OR], 4.3; 95% CI, 1.06–17.48; *P* = 0.04), lower admission levels of fibulin-1 (OR, 0.99; 95% CI, 0.98–0.1; *P* = 0.04) and fibulin-5 (OR, 0.98; 95% CI, 0.97–0.1; *P* = 0.02) were predictors of NSTEMI (TABLE 2).

The ROC curve analysis revealed the cutoff value of 105.6 µg/ml for fibulin-1 levels on admission (sensitivity, 71%; specificity, 75%; area under the ROC curve, 0.78; *P* <0.001) and 49.4 ng/ml for fibulin-5 levels on admission (sensitivity, 84%; specificity, 78%; area under the ROC curve, 0.84; *P* <0.001) to exclude NSTEMI (FIGURE 1).

DISCUSSION The present study aimed to investigate the role of fibulin-1 and -5 in discriminating between patients with noncardiac chest pain and those with NSTEMI in the emergency setting. We found that both glycoproteins are negative predictors for the presence of NSTEMI. Our study also showed that admission values of both parameters facilitate decision making and can be used to exclude NSTEMI with a high sensitivity and specificity in patients presenting to the emergency department with acute chest pain.

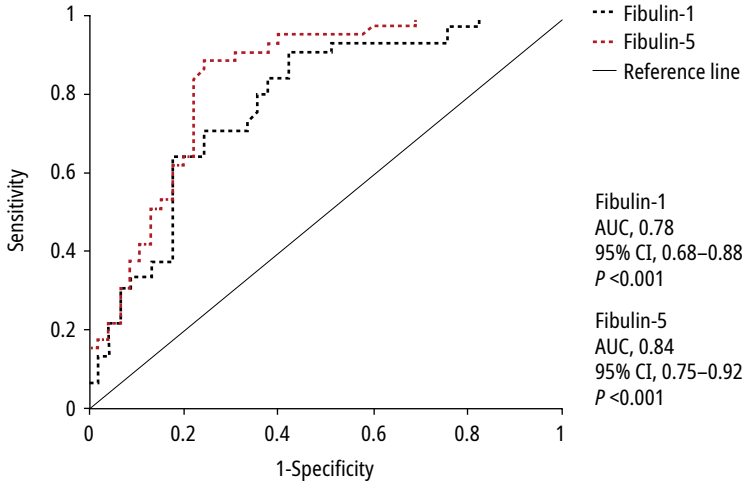

FIGURE 1 Receiver operating characteristic curve analysis showing the performance of fibulin-1 and fibulin-5 in excluding non–ST-segment elevation myocardial infarction in the emergency setting

Abbreviations: AUC, area under the curve

Previous studies reported that the identification of patients with true ACS in the emergency setting is not only critical for rapid revascularization of high-risk patients but also for detecting patients with noncardiac chest pain who should be spared unnecessary invasive procedures as well as anticoagulant and antiplatelet treatment, because it is known that this type of chest pain does not affect long-term mortality.[7] Moreover, the management of patients with chest pain represents a major burden to healthcare; therefore, reducing treatment costs, including the cost of unnecessary hospitalizations, drug treatments, and diagnostic interventions in patients without coronary artery disease, should be one of the goals of healthcare providers.[8] A safe and rapid identification of patients with or without an ACS is the subject of ongoing research aiming at establishing a unique surrogate marker to exclude myocardial infarction, particularly in the emergency setting.[8,9]

Recently, along with the symptoms of ischemia and electrocardiographic changes accompanying acute ischemia, high-sensitivity troponin, copeptin, cardiac myosin–binding protein C, and heart-type fatty acid–binding protein have attracted the attention of investigators attempting to determine potential diagnostic markers for acute NSTEMI. Among these markers, high-sensitivity troponin has been shown to be the most useful in excluding NSTEMI early at presentation, with a reported positive predictive value of 96% for excluding acute myocardial infarction by the third hour of symptom onset.[10,11] However, the exact cutoff value for high-sensitivity troponin to be used as a rule-out test is unclear, and it is still controversial whether a cutoff value lower than the 99th percentile is adequate for identifying patients with noncardiac chest pain.[12,13] Moreover, older age and chronic renal disease, which are relatively common in patients with ACS, have been shown to affect high-sensitivity troponin levels.[14,15] Heart-type fatty acid–binding protein has also been recognized as an early marker of myocardial damage and necrosis. A recent trial indicated that it has a higher sensitivity compared with cardiac troponin I and high-sensitivity troponin I, particularly during the first 3 hours of symptom onset. However, its specificty is lower than that of high-sensitivity troponin-I assay.[16] Some emerging markers of myocardial damage, such as circulating microRNAs, also hold promise in the diagnosis of ACS.[17] However, further research is needed before they can be recommended for routine use in patients with acute chest pain.

Considering the above evidence, several precautions need to be considered when using high-sensitivity troponin. Given its limitations in excluding acute NSTEMI, novel biomarkers with a potential for use as a rule-out test that would enable rapid decision making are required to improve the diagnostic performance of high-sensitivity troponin in NSTEMI.

Fibulin-1 is an extracellular matrix glycoprotein, which is normally present at high concentrations in blood. Human atherosclerotic lesions are rich in fibulin-1, and this protein is assumed to be involved in thrombotic complications of atherosclerosis. In addition, fibulin-1 is a fibrinogen-binding protein and its deposition in atherosclerotic lesions and fresh thrombi usually overlaps with the accumulation of fibrinogen.[18] Several reports have shown that an interaction between plasma fibrinogen and fibulin-1 following vascular injury promotes platelet adhesion, which over time leads to platelet plug formation.[19,20] As a member of the fibulin family of extracellular glycoproteins, fibulin-1 also constitutes a distinct component of the vessel walls. Kotska et al[21] have shown that targeted inactivation of the fibulin-1 gene in mice leads to massive hemorrhage due to dilation and rupture in the endothelial lining of the vessel wall. In light of those findings, we suggest that fibulin-1, as a component of the endothelium, might be essential in endothelial function and that fibulin-1 deficiency might contribute to endothelial dysfunction.[21] Our findings indicate that the blood levels of fibulin-1 measured on admission are lower in patients with NSTEMI compared with those in patients with noncardiac chest pain. This is likely caused by the depletion of fibulin-1 stored in the extracellular matrix of the coronary artery wall during the acute phase of NSTEMI. Another explanation for lower fibulin-1 levels in patients with NSTEMI is that the lack of fibulin-1 might contribute to the development of endothelial dysfunction, which is almost always present in atherosclerotic lesions, and thus the lower fibulin-1 levels in

these patients may reflect the preexisting endothelial dysfunction.

Fibulin-5 is another extracellular matrix glycoprotein investigated in this study, with similar properties to those of fibulin-1. A study on mice demonstrated that fibulin-2 and -5 are involved in the development of internal elastic lamina of the vessel wall and both proteins protect against vascular damage.[4] In patients with hepatocellular carcinoma, fibulin-5 has been shown to downregulate the expression of matrix metalloproteinase 7, an enzyme that is involved in matrix degradation within atherosclerotic lesions, thus leading to plaque destabilization.[22,23] There is also evidence that the upregulation of fibulin-5 through a hypoxia-inducible factor 1–dependent mechanism regulates endothelial cell adhesion, motility, and proliferation, which are components of proper endothelial function.[24] The downregulating effect of fibulin-5 on the expression of matrix metalloproteinase 7 as well as its role in endothelial function may explain why fibulin-5 levels are lower in patients with NSTEMI compared with those of patients with noncardiac chest pain.

With this background in mind, we suggest that the adequate levels of fibulin-1 and -5 are required to protect the vascular wall against various types of damage and to ensure the proper function of the endothelium. Therefore, the deficiency of these proteins might be associated with the development of NSTEMI, and their higher levels might be used as a rule-out test in patients presenting to the emergency department with acute chest pain. More comprehensive studies are needed to further elucidate the complex mechanisms by which fibulin-1 and -5 exert their effects in patients with ACS. Nevertheless, this preliminary study provides the basis for future research investigating the diagnostic role of both proteins in this population. It should be noted that fibulins, as extracellular matrix glycoproteins, are located in various tissues and organs. Changes in blood concentrations of fibulins have been reported in numerous clinical settings, including in patients with intracerebral hemorrhage, chronic obstructive pulmonary disease, aortic aneurysm, peripheral vascular disease, demyelinating neuropathy, acute pulmonary embolism, malignancies, and pelvic organ prolapse.[25-29] The presence of any of these conditions in a patient with acute chest pain may influence the diagnostic potential of fibulins. Therefore, our findings have to be interpreted with caution.

The present study has several limitations. First, the study design was cross-sectional and patient allocation was nonrandomized. We did not examine the angiographic images of patients in detail and we did not assess a correlation between fibulin-1 levels and thrombotic burden. In addition, we did not study the prognostic value of fibulin-1 and -5 for major adverse cardiac events. A comprehensive analysis of the thrombus load and its relation to the fibulin-1 level might help elucidate the mechanism underlying lower fibulin-1 levels in patients with NSTEMI. Moreover, the role of the fibulins in unstable angina and their value for discriminating patients with unstable angina from those with noncardiac chest pain should be addressed in future studies.

In conclusion, to our knowledge, this is the first study to demonstrate that members of the fibulin family of extracellular glycoproteins, fibulin-1 and fibulin-5, might be used for excluding acute NSTEMI in patients admitted to the emergency department with acute chest pain. Our findings showed that admission levels of fibulin-1 and -5 are lower in patients with NSTEMI than those in patients with noncardiac chest pain. For patients with acute chest pain, admission fibulin-1 levels higher than 105.6 µg/ml and admission fibulin-5 levels higher than 49.4 ng/ml may help exclude NSTEMI, in conjunction with troponin measurements. The sensitivity and specificity of the fibulins in our study were acceptable, but they should be confirmed in larger populations with multiple comorbidities. We suggest that both fibulin-1 and -5 could be used as an adjunct test to the troponin measurement for excluding NSTEMI.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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