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Plasma matrix metalloproteinase-9 level in prediction of myocardial fibrosis improved by magnetic resonance imaging in patients with hypertrophic cardiomyopathy

Samet Sevinc, Ömer Çelik, Ali Rıza Demir, Mete Cemek, Mehmet Altunova

Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital, İstanbul, Türkiye

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ABSTRACT

Objectives: This study aimed to compare plasma matrix metalloproteinase-9 (MMP-9) levels of hypertrophic cardiomyopathy (HCM) patients with and without fibrosis.

Patients and methods: Fifty-three HCM patients (33 males, 20 females; mean age: 52.4±10 years; range, 42 to 63 years) diagnosed by transthoracic echocardiography and cardiac magnetic resonance imaging (CMR) between January 2015 and March 2018 were included in the prospective study. They were divided into two groups according to CMR: patients with and without fibrosis. Plasma MMP-9 levels were compared.

Results: In this study, serum MMP-9 levels were significantly higher in HCM patients with myocardial fibrosis in CMR than those without fibrosis (p<0.001). Left ventricular mass index (OR=1.056, 95% CI: 1.004-1.112, p=0.035) and MMP-9 levels (OR=1.031, 95% CI: 1.013-1.049, p=0.003) were independent predictors of myocardial fibrosis.

Conclusion: Serum MMP-9 level has high sensitivity and specificity for prediction of myocardial fibrosis on CMR in HCM patients. It is known that myocardial fibrosis is associated with major adverse cardiac events. Therefore, it would be appropriate to closely monitor HCM patients with high serum MMP-9 levels.

Keywords: Cardiomyopathy, fibrosis, hyperthrophic, magnetic resonance imagination, MMP-9.

Pathologic events that occur in the heart muscle are usually called cardiomyopathy. Cardiomyopathy may occur due to systemic diseases such as valve disease (aortic stenosis and mitral regurgitation) and hypertension. Cardiomyopathies arising from the heart muscle itself are called primary cardiomyopathy. Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, and restrictive cardiomyopathy are examples of primary cardiomyopathies.

Hypertrophic cardiomyopathy is a primary heart muscle disease that occurs in the absence of another cardiac or systemic disease to cause hypertrophy, usually showing increased contractile function, involving mostly the interventricular septum of the undilated left ventricle and causing myocardial hypertrophy. Although HCM can be observed at any age, it most commonly occurs between 40 and 50 years of age. The disease affects males and females alike. Its general prevalence in the population is 0.2%, and it is the most common of the inherited cardiac disorders. Mortality is high in younger patients. Although the majority of HCM patients are asymptomatic, they are usually diagnosed during routine screening of relatives with HCM. The first symptom of patients may be sudden cardiac death. Annual mortality due to HCM is 1%, and mortality is two to four times higher annually in cases diagnosed under 14 years of age.[1,2]

Matrix metalloproteinases (MMPs) are primary matrix-destructive proteases that have the ability to degrade all protein components of the extracellular

Corresponding author: Samet Sevinc, MD. Mehmet Akif Ersoy Göğüs Kalp ve Damar Cerrahisi Eğitim Araştırma Hastanesi, Kardiyoloji Kliniği, 34303 Küçükçekmece, İstanbul, Türkiye
E-mail: sametsevincdr@gmail.com

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matrix. They are members of the zinc- and calcium-dependent endopeptidase family and are characterized by three histidine residues that bind a zinc ion in the catalytic site. Matrix metalloproteinases are also divided into six categories according to their substrate recognition and cleavage mechanism: collagenases, stromelysins, matrilysins, gelatinases, membrane-bound MMPs, and MMPs without group designation. Gelatinases have two types of members: MMP-2 (gelatinase A) and MMP-9 (gelatinase B).[3]

Cardiac magnetic resonance (CMR) imaging studies have demonstrated that myocardial fibrosis can be visualized by late gadolinium enhancement (LGE). However, CMR is expensive, often not available, and not feasible in patients with ferromagnetic implants or claustrophobia. Thus, alternative biomarkers for myocardial fibrosis are needed. This study aimed to examine the association between serum levels of MMP-9 and myocardial fibrosis detected by cardiac magnetic resonance imaging (CMR) in individuals diagnosed with HCM.

PATIENTS AND METHODS

This prospective included 53 patients (33 males, 20 females; mean age: 52.4±10 years; range, 42 to 63 years) who were diagnosed with HCM by echocardiography at the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital, Department of Cardiology, between January 2015 and March 2018. Patients with left ventricular (LV) ejection fraction <50%, those undergoing cardiac surgery, and those who had chronic kidney disease were excluded. Echocardiography was performed in all patients who were compensated. A written informed consent was obtained from each patient. The study protocol was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital Ethics Committee (date 10.04.2018, no: 2018-10). This study was performed in accordance with the principles of the Declaration of Helsinki.

A 12-lead electrocardiogram was performed at 25 mm/sec with the patient at rest in supine position. Resting heart rate was then measured from electrocardiogram data. The measurement of the QRS complex time and PR interval (determined by the largest values and recorded from surface vectors) was performed by experienced cardiologists focused on patients' echocardiographic characteristics.

Blood samples for plasma MMP-9 level were taken from the antecubital vein and collected in EDTA tubes placed on ice. Each pooled sample was centrifuged at 2000 g for 5 min and at 4°C for 30 min. Then the separated plasma was kept at −40°C until the observation time. The MMP-9 level was measured with an assay device (Roche Diagnostics GmbH, Mannheim, Germany).

Images were acquired using 1.5 T scanners (MAGNETON Aera; Siemens Healthcare, Erlangen, Germany) with full myocardial coverage. Balanced steady-state free-precession sequences were used to obtain breath-hold cine images in three long-axis planes, followed by a contiguous stack of short-axis slices from the atrioventricular ring to the apex. Late enhancement images were acquired 10 min after the administration of 0.1 mmol/kg intravenous gadolinium contrast agent (gadopentetate dimeglumine/gadobutrol; Bayer AG, Berlin, Germany) with an inversion recovery-prepared gradient-echo sequence. Inversion times were optimized to null normal myocardium with images acquired in two orthogonal phase-encoding directions to exclude artefact.

Images were transferred to a workstation (Leonardo; Siemens Medical Solutions, Erlangen, Germany) for analysis. For the functional analysis, a commercially available software program, Argus (Siemens Healthcare, Erlangen, Germany), was used. The endocardial and epicardial borders were traced manually using both software systems, and functional analysis was performed. Using the Argus (Siemens Healthcare, Erlangen, Germany) software for each study, the end-diastolic and end-systolic phases were determined. For the detection of each phase, the largest and narrowest diameters of the ventricular cavity at the middle of the ventricle were used. The endocardial and epicardial borders were traced manually in short axis images in both phases. The borders of the endocardium were traced using the intensity difference between the chamber when filled with blood and the moderate intensity of the myocardium. The papillary muscles were included in the LV volumetric analysis. While the epicardial border was being detected, the interventricular septum was included in the LV volume. The most basal slice that was surrounded by at least 50% of the myocardium with filled blood was defined as the basal segment of the left ventricle. This was included in the LV chamber volume. The apex was defined as the last slice with a visible lumen throughout the entire cardiac cycle. The end-systolic

volume (ESV), end-diastolic volume (EDV), and ejection fraction were determined according to the Simpson's rule. The elapsed time from inputting of the data to obtaining the results was calculated for each patient.

The CMR images were reanalyzed and documented using the 17-segment cardiac model recommended by the American Heart Association to improve standardization of the results. The left ventricle was evaluated from the short-axis images from basal, mid, and apical segments. The basal and mid cavity were divided into six equal segments: anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral. The apical segment was divided into four segments: anterior, septal, inferior, and lateral. The apical cap was termed the apex and constituted the 17th segment. Left gadolinium enhancement, validated by a visual assessment and each segment on a two-point scale (segmental fibrosis score; 0= absent LGE, 1= present LGE), was graded using the Kaandrop method and with employee-owned linear frequencies and nonischemic dilated cardiomyopathy increasing irregularly in patients. The cardiac fibrosis index was calculated by the algorithm of percentage of fibrotic segments: (fibrotic segments/17) ×100. Patients were subgrouped based on the presence and absence of fibrosis in any segment of the left ventricle.

Statistical analysis

All analyzes were performed using the IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The variables were examined using visual (histograms and probability plots) and analytical methods (the Kolmogorov-Simirnov test) to determine whether they were normally distributed. Descriptive analyses were presented with the values and standard deviations for normally distributed variables and with median (interquartile range) for nonnormally distributed variables. Comparison of parametric values between the two groups was done with the independent sample t-test. Comparison of nonparametric values between the two groups was done with the Mann-Whitney U test. Categorical variables were compared with the chi-square test. Spearman's test and point biserial correlation coefficient were calculated to examine the relationship between the variables. Logistic regression analysis was used to evaluate predictors of myocardial fibrosis in patients with HCM. Variables with a p-value <0.1 in univariate analysis were included in the backward stepwise multivariate logistic regression analysis model, and odds ratios (ORs) for 95% confidence intervals (CIs) were calculated. Receiver operating characteristic curve analysis was drawn for MMP-9 to predict the presence of myocardial fibrosis. Sensitivity and specificity values were presented when a significant cutoff value was observed. A two-way p-value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical patient characteristics are listed in Table 1. Patients with myocardial fibrosis had high wall thickness (p=0.017) and low LV ESV (p=0.007). There was no difference between the groups regarding age, sex, incidence of hypertension, diabetes, history of coronary artery disease, LV mass, LV outflow trace gradient, and LV EDV. Serum MMP-9 levels were found to be significantly higher in the fibrosis group compared to the nonfibrosis group (1618±62 vs. 1531±50, p <0.001; Table 2). In the HCM group, MMP-9 was positively correlated with the number of regions with LGE (r=0.649, p<0.001).

Table 1
Graphical and clinical patient characteristics in HCM (n=53)

Variables	n	%	Mean±SD
Age (year)			52.4±10
Sex			
Male	33	62.2	
Hypertension	22	41.4	
Diabetes mellitus	11	20.7	
CAD	11	20.7	
Familial HCM	4	7.5	
LVOT gradient	16	30.1	
LV mass (g/m^2)			97.7±16
LV EF (%)			70.7±9
LVEDV (mL/m^2)			74.6±11
LVESV (mL/m^2)			20.7±5
LGE	25	47.2	
MMP-9 (ng/mL)			1572.5±74

HCM: Hypertrophic cardiomyopathy; SD: Standard deviation; CAD: Coronary artery disease; LVOT: Left ventricular outflow tract; LV: Left ventricle; LVEDV: Left ventricle end-diastolic volume; LVESV: Left ventricle end-systolic volume; LGE: Late gadolinium enhancement; MMP-9: Matrix metalloproteinase 9.

Table 2
Comparison of demographic data according to the presence of myocardial fibrosis

	Fibrosis + (n=25)			Fibrosis – (n=28)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			51.8±12			52.8±9	0.729
Sex							
Male	16	64		17	60.7		0.807
NYHA class I, II, III, IV	12	48		17	60.7		0.390
Hypertension	15	60		16	57.1		0.835
Diabetes mellitus	22	88		20	71.4		0.183
CAD	17	68		25	89.2		0.090
Family history	22	88		27	96.4		0.333
LVOT gradient	9	36		7	25		0.550
Angina pectoris	15	60		24	85.7		0.060
Maximal LVWT (mm)			23.1±3			21.1±3	0.017
LV mass (g/m^2)			101.7±15			94.2±16	0.090
LVEDV (mL/m^2)			73.2±9			76±12	0.362
LVESV (mL/m^2)			18.8±4			22.4±4	0.007
LV EF (%)			68.5			72.6	0.122
LGE			2.9±1.3			0	<0.001
MMP-9 (ng/mL)			1618±62			1531±50	<0.001

SD: Standard deviation; NYHA: New York Heart Association; CAD: Coronary artery disease; LVOT: Left ventricular outflow tract; LVWT: Left ventricular wall thickness; LV: Left ventricle; LVEDV: Left ventricle end-diastolic volume; LVESV: Left ventricle end-systolic volume; EF: Ejection fraction; LGE: Late gadolinium enhancement; MMP-9: Matrix metalloproteinase 9.

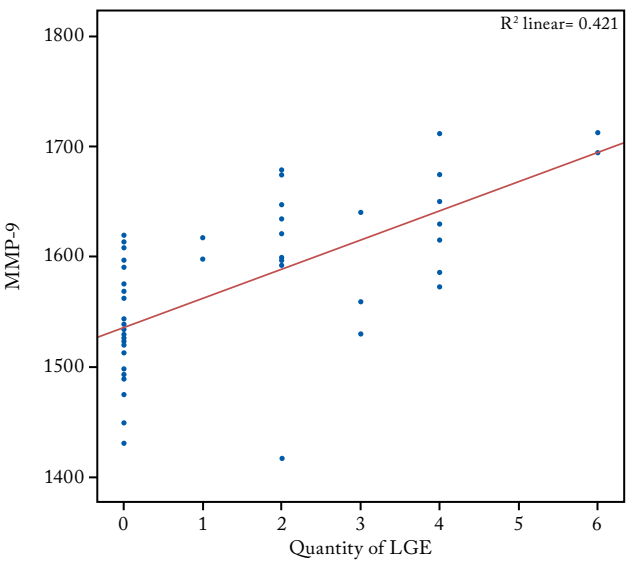

Figure 1. Myocardial correlation graph with serum MMP-9 level between the number of areas with fibrosis.
MMP-9: Matrix metalloproteinase 9; LGE: Late gadolinium enhancement.

There was a mildly significant correlation between MMP-9 levels and LVESV (r=–0.350, p=0.010; Figure 1).

Significant univariate predictors of myocardial fibrosis were history of coronary artery disease, LV mass index, and MMP-9. The results of the

Table 3
Left ventricular mass index, LVESV, and MMP-9 ORs

	OR	95% CI	*p*
LVMI	1.056	1.004-1.112	0.035
CAD	2.098	0.244-1.834	0.500
LVESV	0.955	0.801-1.139	0.606
MMP-9	1.031	1.013-1.049	0.003

LV: Left ventricle; LVESV: Left ventricle end-systolic volume; MMP-9: Matrix metalloproteinase 9; ORs: Odds ratios; CI: Confidence interval; LVMI: Left ventricle mass index; CAD: Coronary artery disease.

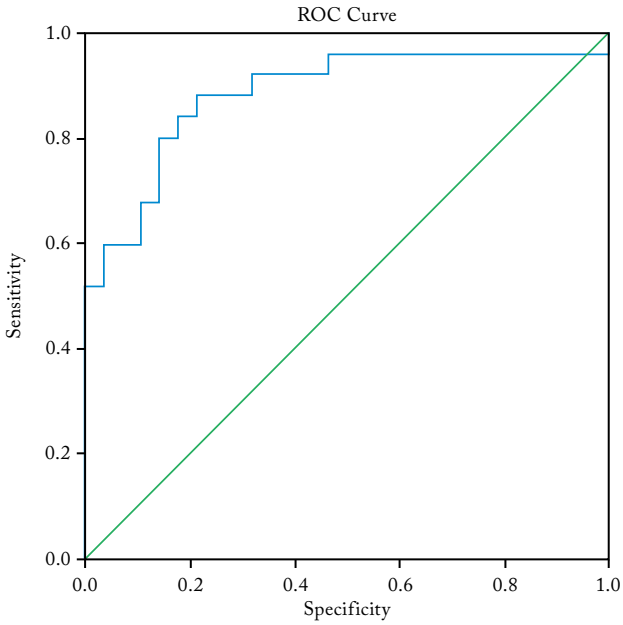

Figure 2. Receiver operating characteristic curve of serum MMP-9 level for detection of myocardial fibrosis in patients with hypertrophic cardiomyopathy (area under the curve=0.884, 95% CI: 0.787-0.981, p<0.001; blue line serum MMP-9 level, green line reference line).

ROC: Receiver operating characteristic; MMP-9: Matrix metalloproteinase 9; CI: Confidence interval.

multivariate logistic regression analysis are presented in Table 3. Receiver operating characteristic analysis yielded a cutoff value of 1580.5% for MMP-9 to predict myocardial fibrosis, with 84% sensitivity and 83% specificity (AUC =0.884, 95% CI: 0.787-0.981, p<0.001; Figure 2).

DISCUSSION

The results of our study indicate a substantial elevation in serum MMP-9 levels in HCM patients exhibiting myocardial fibrosis detected by CMR in comparison to those who did not display fibrosis. Additionally, a noteworthy correlation was found between interventricular septum thickness, as identified by CMR, and cardiac fibrosis. Furthermore, the study demonstrated a positive correlation between the serum MMP-9 level and the quantity of myocardial fibrosis of the left ventricle.

Hypertrophic cardiomyopathy is a hereditary cardiovascular disease characterized by myocardial hypertrophy and impaired diastolic function, which can result in adverse clinical outcomes, including heart failure, arrhythmias, and sudden cardiac death.[1] Myocardial fibrosis, the deposition of excess collagen in the myocardial interstitium, is a common feature of HCM and contributes to the progression of disease.[2] Cardiac magnetic resonance imaging has emerged as a reliable tool for detecting and quantifying myocardial fibrosis in HCM patients, and its role in risk stratification and management has been well-established.[3] The presence and extent of myocardial fibrosis detected by CMR have been shown to correlate with poor clinical outcomes, including heart failure, ventricular arrhythmias, and sudden cardiac death, providing important prognostic information for HCM patients.[4] Consequently, the identification of fibrosis-related factors has become a major research focus, as these may serve as potential therapeutic targets to mitigate disease progression and improve patient outcomes. Current guidelines recommend the use of CMR to assess the presence and extent of myocardial fibrosis in HCM patients, with fibrosis over 15% indicating a high risk of sudden cardiac death and consideration for implantable cardioverter-defibrillator placement.[5] As a consequence, there has been an escalation in the significance attributed to factors related to fibrosis, alongside an increase in efforts aimed at identifying the parameters that could predict the presence and extent of myocardial fibrosis in HCM patients.

Matrix metalloproteinases are a group of endopeptidases that require zinc and are involved in tissue remodeling processes that include the degradation of the collagen network in cardiovascular disease. Among the MMPs, MMP-9, also called type IV collagenase or gelatinase B, is a key player in the tissue remodeling of the extracellular matrix, particularly in the migration of cardiac fibroblasts. Prior research has revealed a relationship between MMP-9 levels and cardiovascular events, including heart failure, atherosclerosis, and myocardial infarction.[6-9] Specifically, Roldán et al.[10] discovered a correlation between cardiac fibrosis and serum MMP-9 levels. Other investigations have also reported a connection between MMP-9 levels and heart failure severity, clinical status deterioration, and atherosclerotic plaque formation and destabilization.[11,12] Additionally, macrophages have been identified as a strong source of MMP-9, and patients with acute myocardial infarction or stable angina exhibited higher levels of MMP-9 in macrophages than those in control groups.[13-15]

Previous research has demonstrated that MMP-9 activity is significantly higher in high-pressure arteries compared to normal-pressure arteries.[16,17] Hypertension-induced cardiac hypertrophy is a key risk factor for various cardiovascular disorders, including diastolic and systolic heart failure, atrial fibrillation, and sudden cardiac death.[18] An association has been reported between increased MMP-9 activity and compensatory hypertrophy of the heart. Specifically, Li et al.[16] observed elevated MMP-9 activity during compensatory hypertrophy in rats with spontaneously elevated blood pressure. Consistent with our results, Münch et al.[19] also found a correlation between MMP-9 and myocardial fibrosis in female HCM patients.

The main limitation of our study is the limited number of patients. Additionally, the visual evaluation of the existence of LGE without using software may be considered another limitation. It should be noted that not all molecules in circulation reflect changes in collagen metabolism at the cardiac level, as collagen is the most abundant protein in the body. Another potential limitation is that we did not evaluate the cardiac tissue concentration of MMPs in our study. Further research with a larger cohort should analyze a broad panel or marker cassette for validation.

In conclusion, the degree of interventricular septum thickness is an important indicator of HCM. Similar to the findings of our study, previous studies have shown that there is a positive correlation between the degree of interventricular septal thickness and the extent of myocardial fibrosis in HCM patients. Specifically, HCM patients with greater degrees of interventricular septal thickness tend to have more extensive myocardial fibrosis. This relationship highlights the importance of monitoring both interventricular septal thickness and the presence of myocardial fibrosis in HCM patients, as both parameters can provide important information for risk stratification and management of the disease.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, writing the article: S.S.; Design: Ö.Ç.; Control/supervision: A.R.D.; Data collection/processing: H.K.; Analysis/interpretation: M.A.; Literature rewiew: S.T.K.; Critical rewiews: A.R.D.; References and fundings: M.C.; Materials: Y.Ö.

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