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Original Article

Association of matrix-metalloproteinase-9 with left ventricular diastolic dysfunction in patients with hepatitis C virus infection

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Abstract: Background and objective: Hepatitis C Virus (HCV) infection and elevated Matrix Metalloproteinase-9 (MMP-9) levels have been individually associated with cardiovascular diseases (CVD). However to date, no study has focused on the combined association of HCV and MMP-9. The aim of this study was to investigate the characteristics of MMP-9 and its correlation with clinical profiles such as echocardiographic variables in HCV-infected patients. Methods and Results: One hundred and thirty HCV-infected patients and 130 healthy controls were enrolled. Serum MMP-9 level was significantly higher in all 130 patients (median 33.54 ng/mL, range 26.29~86.24 ng/mL) compared to controls (median 25.66 ng/mL, range 18.04~42.91 ng/mL, P = 0.004). E, E', and E/A were significantly lower in HCV-infected patients while E/E' was significantly higher. Simple regression analysis demonstrated a statistically significant linear correlation between MMP-9 vs. E/E' (r = 0.237, P = 0.025), MMP-9 vs. A (r = 0.158, P = 0.031), and MMP-9 vs. LVEF (r = -0.289, P = 0.028). Independent correlates of MMP-9 levels was E/E' ratio (β' = 0.073, P = 0.031) after adjusting for A, LVEF and age (OR: 1.97, 95% CI: 1.25~2.74, P < 0.001) for the multivariate model. Conclusion: Elevated serum MMP-9 levels in HCV-infected patients correlated with E/E' ratio, which suggests a subclinical association between MMP-9 levels and left ventricular diastolic dysfunction (LVDD) in HCV-infected patients.

Keywords: MMP-9, left ventricular diastolic dysfunction, HCV infection

Introduction

Over the past several decades, studies have focused on the association between Hepatitis C virus (HCV) and cardiovascular diseases (CVD) including cardiomyopathies [1-3], coronary artery diseases (CAD) [4, 5] and carotid atherosclerosis [6, 7]. Our previous investigations found that patients with HCV infection exhibited evidence of left ventricular diastolic dysfunction (LVDD) [8, 9] and inflammation reflected by serum tumor necrosis factor (TNF)-α might play a role in the pathogenesis of LVDD [10].

HCV infection is recognized to cause chronic immune stimulation leading to inflammatory response and cytokine production [11] which could potentially cause adverse cardiovascular outcomes. Individuals with HCV infections are found to be at increased risk for CVD-related morbidity and mortality [12]. The knowledge about risk factors associated with CVD in HCV-infected patients is of crucial importance to the understanding of the future risk of CVD and in the evaluation of possible effects of future screening and intervention against CVD risk factors.

Matrix Metalloproteinase 9 (MMP-9), one of the most investigated MMPs, is believed to be involved in ventricular remodeling processes [13], atherosclerosis [14], plaque rupture [15, 16] and fibrosis in CVDs [17]. Previous studies have provided evidence that MMP-9 can be of diagnostic importance in early CAD [18, 19] and is also elevated in CAD patients with impaired heart functions [20-22]. However, the features

and clinical relevance of MMP-9 in HCV-infected patients have not been fully addressed.

Materials and methods

The present study was approved by the Ethics Committee of Shanghai Tenth People's Hospital, Tongji University School of Medicine, and complied with the World Medical Association Declaration of Helsinki. All subjects gave their informed consent for participation in the study, which was approved by the Ethics Committee of Shanghai Tenth People's Hospital, Tongji University School of Medicine (SHSY-IEC-KY-4.0/16-41/02).

Subjects

One hundred and thirty HCV infected patients were recruited from Shanghai Tenth People's Hospital and Shanghai Tenth People's Hospital Chongming Branch from January 2014 to May 2016 based on the following criteria: positive for serum HCV RNA and anti-HCV antibody. Patients with other types of hepatitis or liver disease of different etiology, liver cirrhosis, HCV infected patients treated with interferon α in the past six months or less, other infectious diseases, overt cardiovascular disease, lung disease, endocrine diseases, renal dysfunction (serum creatinine level > 2.0 mg/dL), pregnant or postpartum women, present or past history of alcohol or drug abuse, or the presence or history of neoplastic diseases were excluded from the study. An identical number of healthy individuals whose age and gender matched with HCV-infected patients were recruited randomly from the general population in a population-based survey of plasma cholesterol levels and served as the control population. All enrolled control subjects had no documented history of chronic systemic diseases including liver disorders, CVD, renal disorders, autoimmune diseases, and neoplastic diseases.

Blood sample collection and analysis

Blood specimens from the patient group were collected under standardized conditions after an overnight fast immediately before the initiation of interferon α treatment and centrifuged at 3,000 g. The separated serum was stored at -80°C until analysis. Serum from the control group was also separated and stored using similar methods. Concentrations of serum MMP-9 were measured using an enzyme linked immunosorbent assay (ELISA) kit (RapidBio, West Hills, CA, USA). HCV RNA was quantified by Cobas Amplicor HCV Test, Version 2.0 (RocheMolecular Systems, Inc., Pleasanton, CA). Anti-HCV antibody was measured by ElAgenHCV Ab Kit (Adaltis Italia S.p.A).

Echocardiography study

All patients had trans-thoracic echocardiography and Doppler examination (Philips Sonos 5500, 2~4 MHz transducer) before interferon α treatment. Two-dimensional echocardiography imaging, and conventional and tissue Doppler imaging (TDI) ultrasound measurements were obtained by two observers. All echocardiography data represent the mean of 3 measurements on different cardiac cycles. The following parameters were analyzed: left ventricular ejection fraction (LVEF), fractional shortening (FS), left ventricular diastolic diameter (LVDd), interventricular septum diastolic thickness (IVSd), left ventricular posterior wall diastolic thickness (LVPWd), peak early diastolic transmitral flow (E), peak late diastolic transmitral flow (A), the E/A ratio, and E-wave deceleration time (DT). The TDI of the mitral annulus movement was obtained from the apical 4-chamber view, and the values were averaged, respectively (E' and A'), and the ratio of E/E' was calculated. The control population was also subjected to echocardiographic evaluation and similar parameters were recorded.

Statistical analysis

All statistical analyses were performed with the statistical package SPSS 12.0.1 (SPSS Inc, Chicago, IL). Categorical data were expressed as proportions (%) and χ^2 test was used to compare proportions. Continuous data are expressed as the mean ± standard deviation or median (range, 25%~75%). Student's t-test or Mann-Whitney U-tests was used to determine differences between groups, where appropriate. Linear regression analysis and multiple logistic forward stepwise regression were performed to evaluate the relationship between MMP-9 and clinical profiles. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study group

One hundred and thirty patients with HCV infection (60 females, 70 males) aged 24 to 74

Table 1. Baseline characteristics of subjects

Variables	Patients (N = 130)	Controls (N = 130)	*P* Value
Height (cm)	167.8±5.4	168.5±5.7	0.310
Weight (kg)	66.9±7.7	68.6±7.1	0.065
SBP (mmHg)	126.6±12.4	127.8±14.1	0.467
DBP (mmHg)	75.3±8.2	74.6±7.4	0.471
TC (mmol/l)*	3.80±0.47	3.66±0.52	*0.024*
Triglycerides (mmol/l)	1.16±0.57	1.20±0.54	0.562
BMI	24.11±3.34	24.3±2.18	0.587
Smoker (n, %)	16, 12.2	18, 13.7	0.861

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TC, total cholesterol. Data are expressed as mean ± SD. *A *P* value of less than 0.05 was considered statistically significant.

Table 2. Clinical characteristics of patients group

Variables	Patients
Duration of hepatitis C (yr; means ± SD)	5.4±2.8
HCV RNA (copies/mL; median (25%~75%))	3.69×10^6 (2.13×10^5~2.96×10^7)
Serum albumin (g/L; means ± SD)	38.52±6.32
AST (IU/L; median (25%~75%))	50.5 (28.2~85.8)
ALT (IU/L; median (25%~75%))	43.5 (25.8~82.5)
LDH (IU/L; means ± SD)	179.8±35.4
Serum creatinine (mg/dl; median (25%~75%))	0.82 (0.69~0.98)
eGFR ($ml{\cdot}min^{-1}(1.73m^{-2})^{-1}$; means ± SD)	95.4±9.5

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; eGFR, estimated glomerular filtration rate.

(51.1±10.6) years were enrolled and 130 gender matched controls aged 25 to 73 (50.9± 11.0) years were also recruited. The baseline characteristics are presented in **Table 1**. Height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglyceride (TG), BMI, and proportion of smokers between groups showed no significant differences. Total cholesterol (TC) level was higher in the HCV-infected group (3.80±0.47 mmol/L versus 3.66±0.52 mmol/L, P = 0.024). The clinical characteristics of the patient group are given in **Table 2**.

Comparison of serum MMP-9 levels and echocardiographic parameters between groups

The level of serum MMP-9 was significantly higher in all 130 patients (median 33.54 ng/mL, range 26.29~86.24 ng/mL) than that in controls (median 25.66 ng/mL, range 18.04~42.91 ng/mL, P = 0.004). Our previous study which enrolled 106 HCV-infected patients demonstrated that mild diastolic dysfunction exists in HCV infected patients [9]. In the present study, E, E', and E/A were lower in HCV-infected patients than in the control group, respectively, and E/E' was higher as shown in **Table 3**.

Correlation of serum MMP-9 levels and echocardiographic variables in HCV-infected patients

Correlation of serum MMP-9 levels and echocardiographic variables was analyzed in the patients group. Univariate echocardiographic correlates of serum MMP-9 levels are presented in **Table 4**. Simple regression analysis demonstrated a statistically significant linear correlation between MMP-9 vs. E/E' (r = 0.237, P = 0.025), MMP-9 vs. A (r = 0.158, P = 0.031), and MMP-9 vs. LVEF (r = -0.289, P = 0.028).

Serum MMP-9 Levels and LV diastolic dysfunction

Patients with E/E' levels > 15 were classified as LVDD and had significantly higher MMP-9 (31.3 ng/mL vs. 9.2 ng/mL, P < 0.001) compared to those with normal diastolic function (E/E' < 8) [23]. There was no statistically significant difference between the control group and HCV-infected patients with normal diastolic dysfunction (P > 0.5). To adjust for the confounding effect of other factors, we performed logistic multivariate analysis on all patients. MMP-9 levels were still associated with E/E' (β' = 0.073, P = 0.031) after adjusting for A, LVEF, and age (OR: 1.97, 95% CI: 1.25~2.74, P < 0.001) for the multivariate model. This is shown in **Table 5**.

Discussion

Our study is the first to investigate the association between MMP-9 and echocardiographic changes in HCV infected patients. The results suggest a subclinical association between

Table 3. Echocardiographic measurements between groups

Variables	Patients (N = 130)	Controls (N = 130)	*P* Value
LVDd (mm)	47.89±4.41	47.79±4.54	0.857
LVPWd (mm)	9.47±1.65	9.28±1.78	0.373
IVSd (mm)	9.74±1.58	9.80±1.54	0.757
E (cm/s)*	69.85±14.50	86.49±13.82	*< 0.01*
A (cm/s)	62.17±11.75	60.44±12.63	0.254
E/A*	1.14±0.48	1.46±0.42	*< 0.01*
DT (ms)	175.5±26.8	176.8±23.4	0.677
E' (cm/s)*	7.34±2.88	9.84±2.74	*< 0.01*
A' (cm/s)	10.45±2.90	10.11±2.85	0.341
E/E'*	9.75±2.38	8.87±2.55	*0.004*
LVEF (%)	64.68±7.34	66.16±6.74	0.092
FS (%)	39.52±4.53	39.19±4.91	0.574

Abbreviations: LVDd, left ventricular diastolic diameter; LVPWd, left ventricular posterior wall diastolic thickening; IVSd, interventricular septum diastolic thickening; E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; E', peak early diastolic annular velocity; A', peak late diastolic annular velocity; E/E', the ratio of E to E'; DT, deceleration time; LVEF, left ventricular ejection fraction; FS, fractional shortening. Data are expressed as mean ± SD. *A *P* value of less than 0.05 was considered statistically significant.

Table 4. Correlation coefficients of linear regression analysis between MMP-9 and echocardiographic parameters in patients group

Variable	Log MMP-9	
	r Value	*P* Value
LVDd (mm)	0.243	0.153
LVPWd (mm)	0.067	0.195
IVSd (mm)	0.534	0.465
LVEF (%)	-0.289	*0.028*
FS (%)	-0.583	0.434
E (cm/s)	0.326	0.347
A (cm/s)	0.158	*0.031*
E/A	0.678	0.596
DT (ms)	-0.841	0.233
E' (cm/s)	0.337	0.197
A' (cm/s)	0.189	0.069
E/E'*	0.237	*0.025*

Abbreviations: LVDd, left ventricular diastolic diameter; LVPWd, left ventricular posterior wall diastolic thickening; IVSd, interventricular septum diastolic thickening; LVEF, left ventricular ejection fraction; FS, fractional shortening; E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; DT, deceleration time; E', peak early diastolic annular velocity; A', peak late diastolic annular velocity; E/E', the ratio of E to E'. *A *P* value of less than 0.05 was considered statistically significant.

MMP-9 levels and LVDD in HCV infected patients. HCV infection stimulates the production of inflammatory cytokines and chemokines [11]. Many studies investigating the relationship between hepatic manifestations of MMP-9 in HCV patients have found elevated MMP-9 levels in the patient group compared to the control group [24, 25]. Pathological accumulation of the extracellular matrix is the main feature of fibrogenesis, which indicates an imbalanced rate of increased matrix synthesis to decreased breakdown of connective tissue proteins which is regulated by the MMPs. The results from our study also show significantly higher levels of MMP-9 in the patient group. Until now, the relationship between cardiovascular manifestations and levels of MMP-9 in HCV patients has not yet been investigated.

Over the years, MMP-9 has proven to be a biomarker of plaque stability as it is involved in atherosclerosis [14] and plaque degradation [15, 16]. MMP-9 also plays a vital role in myocardial remodeling, thus any structural or functional changes of the myocardium is reflected by elevated MMP-9 levels [26] and these changes can be diagnosed and evaluated by echocardiography. Studies investigating MMP-9 levels in heart failure patients have concluded that elevated MMP-9 levels are associated with cardiac dysfunction that is reflected by lower LVEF [27, 28] and higher End Systolic Volume (ESV) [27], severe LVDD [28], altered E/E' ratio [28], advanced New York association class, and can be used as a prognostic marker for adverse left ventricular remodeling [27]. Other studies investigating the role of MMP-9 in CAD patients showed that elevated MMP-9 are associated with severe LVDD [20, 21], altered E/E' [20, 21] ratio, and can provide evidence of adverse left ventricular remodeling [29-31]. Furthermore, it has been seen that MMP-9 deletion may reduce age-related myocardial stiffness, therefore improving LVEF [32], MMP-9 deletion, and macrophage MMP-9 overexpression, could attenuate cardiac remodeling in a mouse model of myocardial infarction [33, 34]. MMP-9 inhibitors have also been seen to attenuate LV remodeling [35]. In studies which assessed the echocardiographic response to cardiac resynchronization therapy (CRT) in chronic heart failure patients with elevated MMP-9 levels, MMP-9 changes in response to CRT [36] predicted baseline left

Table 5. Multivariable linear regression for log MMP-9 as dependent variable

Variable	β	β'	*P* value
Age (y)	0.032	0.041	0.142
LVEF	0.026	0.057	0.073
A	0.037	0.084	0.098
E/E'*	0.079	0.073	*0.031*

Abbreviations: LVEF, left ventricular ejection fraction; A, peak late diastolic transmitral flow; E, peak early diastolic transmitral flow; E', peak early diastolic annular velocity; E/E', the ratio of E to E'; β: Regression coefficient; β': Standardized coefficient. *A *P* value of less than 0.05 was considered statistically significant.

atrial end diastolic diameter and LV end-diastolic diameter changes [37]. However, the clinical relevance of MMP-9 in left ventricular function of HCV-infected patients and whether MMP-9 is an appropriate surrogate cardiovascular risk marker in HCV-infected population have not been fully addressed.

We further evaluated the correlation between MMP-9 and morphological and functional changes of LV with a Doppler echocardiogram in patients with HCV infection. We did not find any correlation between MMP-9 levels and LV systolic function as evaluated by LVEF and FS. Besides aging, many factors such as A, LVEF, and E/E' also have a major contribution in LVDD. The relationship between elevated MMP-9 levels and LV diastolic dysfunction was further analyzed. Multivariate analysis on all patients to adjust for confounding effects showed that MMP-9 levels were still associated with E/E'. The presence of LVDD, evaluated by E/E', has been found to be useful for risk assessment in patients with LV remodeling [23] and is a frequent finding in patients with HCV infection [9, 10]. It is believed that LVDD can be present for several years before heart failure becomes clinically evident [38]. Therefore early diagnosis and treatment may be important in preventing irreversible structural alterations and systolic dysfunction, thereby improving the patient's prognosis. The present data demonstrate that MMP-9 levels possibly associate with the risk cardiovascular events in the HCV-infected population. The results suggest a subclinical association between MMP-9 levels and LVDD in HCV infected patients.

Some limitations of our study deserve to be discussed. First, patients were enrolled from only two centers and the number of patients was relatively small. Second, follow-up data showing that elevated MMP-9 levels are associated with adverse cardiac effects in HCV-infected patients is missing.

To conclude, we found that elevated serum MMP-9 levels in HCV-infected patients correlated with the E/E' ratio, which suggests a subclinical association between MMP-9 levels and left ventricular diastolic dysfunction in HCV infected patients. The findings of the present study have important implications for HCV-infected patients. The application of MMP-9 as a cardiovascular risk marker should be evaluated in CVD patients in conjunction with HCV infection. The effective therapeutic strategies should be studied more thoroughly in the future both on experimental and clinical grounds.

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Disclosure of conflict of interest

None.

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