CORRELATION OF SERUM TIMPS AND MMPS WITH CARDIAC STRUCTURE AND FUNCTIONAL PARAMETERS IN PATIENTS WITH ESSENTIAL HYPERTENSION

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ABSTRACT

Objective*: To analyze the correlation between serum tissue inhibitors of metalloproteinase (TIMPs), matrix metalloproteinases (MMPs), and cardiac structural and functional parameters in patients with primary hypertension.*

Methods: *This study was performed with the approval of the hospital ethics committee. One hundred and thirty-six patients with primary hypertension – who were treated at our hospital from September 2017 to March 2019 – were randomly selected. Levels of TIMP-1 less than 180 ng/ml were the TIMP-1 normal group (89 cases) and the levels greater than 200 ng/ml were the TIMP-1 elevated group (47 cases). Levels of MMP-9 less than 150ng/ml were normal MMP-9 groups (87 cases), and levels higher than 150ng/ml were the elevated MMP-9 group (49 cases). A cardiac-function tester was used to detect the level of each cardiac structural index [ventricular septal thickness (IVSTd) and left atrial inner diameter (LAD)] and cardiac function index [E peak/A peak velocity ratio of diastolic function (E/A), left ventricular ejection fraction (LVEF)] in each group. The Pearson correlation test was used to analyze the correlation between serum TIMPs, MMPs, and cardiac structure and function indexes in patients with primary hypertension.*

Results: *In comparison to the normal TIMP-1 group, the IVSTd and LAD levels of the patients in elevated TIMP-1 group were significantly increased (P<0.05) and the levels of E/A and LVEF were significantly decreased; these differences were statistically significant (P<0.05). Compared with the normal MMP-9 group, the IVSTd and LAD levels of the patients in the elevated MMP-9 group were significantly increased (P<0.05), the levels of E/A and LVEF were significantly decreased, and the differences were statistically significant (P<0.05). According to the Pearson correlation test, the levels of TIMP-1 and MMP-9 were clearly positively correlated with cardiac structural indicators such as IVSTd and LAD, but were negatively correlated with cardiac functional indicators such as E/A and LVEF (P<0.05).*

Conclusion: *The serum MMP-9 and TMIP-1 levels are abnormal in patients with hypertension and are closely related to the occurrence, development, and prognosis of arteriosclerotic disease in center and peripheral arterial hypertension patients.*

Keywords: *Primary hypertension, TIMPs, MMPs, cardiac structure, functional indicators, correlation.*

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Introduction

Primary hypertension occurs when the exact cause of high blood pressure cannot be ascertained. With the development of the economy and the improvement in people's living standards, the instances of hypertension are increasing year on year. Statistics show that more than 1.5 billion patients suffer from hypertension worldwide, and more than 8 million people die of hypertension-related diseases each year, which can have a serious impact on people's lives and families[(1)]. According to the American Hypertension Association, hypertension is a progressive cardiovascular syndrome with many causes that can lead to changes in function and structure of the heart and blood vessels[(2)]. With increases in blood pressure, the load pressure on the heart increases significantly, which can alter the myocardium, leading to changes in cardiac function[(3)]. Studies have found that changes in cardiac structure occur mainly in the

left ventricle, whose hypertrophy is considered to be a fundamental high-risk factor for cardiovascular events[4]. Cardiac remodelling is related to hypertrophy and the apoptosis of myocardial cells; further, the extracellular matrix of myocardium plays an important role in maintaining the arrangement of myocardial cells, coordinating myocardial contractility, and maintaining left-ventricular configuration[5].

In this study, patients with primary hypertension treated at our hospital from September 2017 to March 2019 were selected as research subjects; their serum tissue inhibitors of metalloproteinase (TIMPs), matrix metalloproteinases (MMPs), cardiac structure and functional indicators were tested and their correlations were analyzed.

Data and methods

General data

This study was performed with the approval of the hospital ethics committee. One hundred and thirty-six patients with primary hypertension – who were treated at our hospital from September 2017 to March 2019 – were randomly selected.

The inclusion criteria were as follows:

• All patients met the diagnostic criteria for primary hypertension according to the World Health Organization/International Hypertension Alliance Hypertension Conference[6];

• Patients whose systolic blood pressure ≥140 mmHg and/or diastolic blood pressur e≥90 mmHg;

• Patients were aged between 25 and 80 years;

• Patients and their family members agreed and provided written informed consent;

• Patient medical records were complete.

The exclusion criteria involved the following:

• Those who had liver, kidney, or cardiac dysfunction;

• Patients with poor mental health;

• Patients with secondary hypertension;

• Lactating or pregnant patients;

• Patients with severe infectious diseases.

The final selected subjects included 86 males and 50 females, aged 25 to 80 years, with an average age of 59.77±5.28 years. Their disease duration spanned from 3 to 11 years, with an average of 6.27±2.63 years. There was no significant difference in the comparison of basic data among patients in each group (P>0.05).

Grouping

Patients with TIMP-1 levels less than 180 ng/ml were selected as the TIMP-1 normal group (89 cases), and those with TIMP-1 levels greater than 200 ng/ml were the TIMP-1 elevated group (47 cases). Further, patients with MMP-9 levels less than 150 ng/ml were the normal group of MMP-9 (87 cases), and those with MMP-9 levels higher than 150 ng/ml were the group with elevated MMP-9 (49 cases).

Observation indicators

All subjects participating in the study were not allowed to drink or eat for more than 10 hours prior to 5 mL of fasting venous blood collection. The collected blood was left at room temperature for 20 min, centrifuged at 3000 r/min for 10 min, then stored in a refrigerator at –80°C for testing.

Cardiac-function testers were used to detect the cardiac structural indicators [Interventricular septum thickness (IVSTd) and left atrial diameter (LAD)], cardiac function indicators [E peak/A peak velocity ratio of diastolic function (E/A) and left ventricular ejection fraction (LVEF)].

The Pearson correlation test was used to analyze the correlation between serum TIMPs, MMPs, and cardiac structure and function indexes in patients with primary hypertension.

Statistical method

Measurement data were compared using the independent sample t-test between two groups; the comparison between multiple groups was performed using a single-factor analysis of variance test.

Count-data comparison was performed using the χ^2 test. The cardiac-function tester was used to detect the levels of cardiac structural indicators and functional indicators of patients in each group.

The Pearson correlation test was used to analyze the correlation between serum TIMPs, MMPs, and cardiac structure and function indexes in patients with primary hypertension.

P<0.05 was considered to be statistically significant. This study used the SPSS18.0 software package for statistical data analysis.

Results

Comparison of cardiac structure between the normal TIMP-1 group and elevated TIMP-1 group

In comparison to the normal TIMP-1 group, the IVSTd and LAD levels of the patients in the elevated TIMP-1 group were significantly increased (P<0.05), as can be seen in Table 1.

Group	Cases (n)	IVSTd (mm)	LAD (mm)
Normal TIMP-1 group	89	9.19±1.29	33.08±2.64
Elevated TIMP-1 group	47	11.07±2.01	36.49±3.52
t		6.621	6.364
P		<0.001	<0.001

Table 1: Comparison of cardiac structure between the normal TIMP-1 group and elevated TIMP-1 group.

Comparison of cardiac function indexes in the normal TIMP-1 group and elevated TIMP-1 group

The results showed that the levels of E/A and LVEF in patients with elevated TIMP-1 were significantly lower than those in the normal TIMP-1 group, and the difference was statistically significant (P<0.05). The results are shown in Table 2.

Group	Cases (n)	E/A	LVEF (%)
Normal TIMP-1 group	89	1.06±0.27	65.36±4.84
Elevated TIMP-1 group	47	0.75±0.18	54.75±4.28
t		7.078	12.639
P		<0.001	<0.001

Table 2: Comparison of cardiac function indicators between the normal TIMP-1 group and elevated TIMP-1 group.

Comparison of cardiac structural indexes in the normal MMP-9 group and elevated MMP-9 group

In comparison to the normal MMP-9 group, the IVSTd and LAD levels of the patients in the elevated MMP-9 group were significantly increased (P<0.05), as can be seen in Table 3.

Group	Cases (n)	IVSTd (mm)	LAD (mm)
Normal MMP-9 group	87	8.22±1.13	36.98±2.03
Elevated MMP-9 group	49	12.29±1.15	34.02±3.65
t		20.038	6.085
P		<0.001	<0.001

Table 3: Comparison of cardiac structural indexes between the normal MMP-9 group and elevated MMP-9 group.

Comparison of cardiac function indexes between the normal MMP-9 group and elevated MMP-9 group

As can be seen in Table 4, the levels of E/A and LVEF in the patients with elevated MMP-9 were significantly lower than those in the normal group with MMP-9, and the differences were statistically significant (P<0.05).

Group	Cases (n)	E/A	LVEF (%)
Normal MMP-9 group	87	1.19±0.27	66.27±6.66
Elevated MMP-9 group	49	0.83±0.18	52.66±4.65
t		8.341	12.662
P		<0.001	<0.001

Table 4: Comparison of cardiac function indexes between the normal MMP-9 group and elevated MMP-9 group.

Correlation of serum TIMPs and MMPs with cardiac structure and functional parameters in patients with primary hypertension

Pearson correlation analysis found that the levels of TIMP-1 and MMP-9 were significantly positively correlated with cardiac structural indicators such as IVSTd and LAD, and significantly negatively correlated with cardiac functional indicators such as E/A and LVEF (P<0.05). The results can be found in Table 5.

Indicators	TIMP-1		MMP-9	
	r	*P*	*r*	*P*
IVSTd	0.475	<0.05	0.768	<0.05
LAD	0.332	<0.05	0.476	<0.05
E/A	–0.154	<0.05	-0.577	<0.05
LVEF	–0.527	<0.05	-0.669	<0.05

Table 5: Correlation analysis.

Discussion

Hypertension is a disease caused by the combined action of multiple genetic and environmental factors, and is characterized by elevated arterial blood pressure, which can affect all systems in a patient's body. The onset of hypertension is insidious and progressive. With the development of the disease and its prolonged incidence, the arterial vascular elasticity of the patient is significantly reduced[7]. Studies have found that long-term sustained increases in blood pressure can promote the occurrence and development of atherosclerosis at all levels, leading to intimal hyperplasia and narrowing of the lumen, reducing the blood volume of target organs such as the heart and brain, and eventually leading to organ modification, threatening patients' lives and health[8]. Therefore, early detection, early diagnosis, and early treatment are of great significance to strengthen the monitoring of hypertension and target organ damage, such as in the cardiovascular system.

At present, attention to the reduction of blood pressure and reducing the risk and mortality of cardiovascular and cerebrovascular diseases caused by

high blood pressure is the focus of prevention and treatment of hypertension, while less attention has been paid to the changes in the heart structure and function of patients with hypertension[9].

Studies have found that when blood pressure rises, the resistance of surrounding blood vessels increases significantly. When blood pressure continues to rise steadily without control, it can cause hypertrophy of the left ventricle, which is considered to be an important indicator of hypertension complications and increased mortality, and is one of the important indicators of myocardial remodelling in patients with hypertension. It is also a major risk factor associated with cardiovascular disease deaths[10-11]. According to relevant literature, changes in the left ventricular configuration can cause decreased systolic function, while hypertension can cause changes in the structure and function of the heart, and abnormal diastolic function precedes systolic function[12-13].

Ventricular remodelling is one of the main pathological mechanisms for the development of several cardiovascular diseases into chronic cardiac insufficiency, including myocardial parenchymal remodelling and myocardial interstitial remodelling. Changes in the quality and quantity of extracellular matrix constituents are an important part of myocardial interstitial remodelling. Under normal circumstances, the synthesis and degradation of collagen in the matrix are regulated by a variety of factors, wherein MMPs play an important role in the accumulation and degradation of extracellular matrix collagen. TIMPs can combine with zymogens of MMPs to inhibit MMP activation and regulate their activity[14-15]. As a member of the MMP family, some studies have suggested that MMP-9 levels are closely related to patients' cardiac function[16].

MMP-9 inhibitors can reduce left ventricular dilatation and maintain left ventricular systolic function. Gronda et al.[17] found – in a study on rats – that MMP-9 knockout rats can significantly delay the expansion of the left ventricular cavity after myocardial infarction. TIMP-1 is an endogenous inhibitor of MMP-9 widely present in tissue and body fluids. According to reports, TIMP-1 levels in patients with hypertension are significantly positively correlated with left ventricular hypertrophy and diastolic dysfunction, that can be used as important markers[18].

In this study, the levels of IVSTd and LAD in patients with elevated TIMP-1 were significantly higher than those in the normal TIMP-1 group, and the levels of E/A and LVEF were significantly lower than those in the normal TIMP-1 group ($P<0.05$). The levels of IVSTd and LAD in patients with elevated MMP-9 were significantly higher than those in the normal MMP-9 group, and the levels of E /A and LVEF were significantly lower than those in the normal MMP-9 group ($P<0.05$). It is suggested that the increase in serum MMP-9 and TIMP-1 levels in patients with hypertension is significantly related to the patient's heart structure and function, which can be used as an important indicator to evaluate the patient's heart health, which consistent with the findings of Gruszka et al.[19].

In summary, abnormal levels of serum MMP-9 and TMIP-1 exist in patients with hypertension, and the levels of MMP-9 and TMIP-1 are closely related to the occurrence, development, and prognosis of arteriosclerotic diseases in patients with hypertension. However, owing to the small number of samples in this research, the results need to be analyzed further.

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