Correlation between high mobility group box 1 protein, tumor necrosis factor-α, and acute coronary syndrome.

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Abstract

This study aims to investigate the relationships between the serum concentrations of High Mobility Group Box 1 (HMGB1) protein and Tumor Necrosis Factor-α (TNF-α), coronary artery lesions, and cardiac function in patients with Acute Coronary Syndrome (ACS). We prospectively followed healthy controls (n=30) and patients with ACS (n=60) who underwent coronary angiography. Serum HMGB1 and TNF-α concentrations were measured by enzyme-linked immunosorbent assay. Serum concentrations of HMGB1 (33.22 ± 16.59 ng/ml in Acute Myocardial Infarction Group (AMIG) and 23.40 ± 12.17 ng/ml in Unstable Angina Pectoris Group (UAPG)) and TNF-α (10.68 ± 4.94 pg/ml in AMIG and 6.37 ± 3.53 pg/ml in UAPG) in patients with ACS prior to standard hospitalization were significantly higher than those of the control group (HMGB1: 12.23 ± 2.74 ng/ml; TNF-α: 2.13 ± 1.26 pg/ml) (p<0.01). The concentrations of HMGB1 (21.67 ± 13.00 ng/ml in AMIG and 18.71 ± 6.92 ng/ml in UAPG) and TNF-α (5.28 ± 3.09 pg/ml in AMIG and 3.71 ± 2.34 pg/ml in UAPG) in patients with ACS post-standardized hospitalization were lower than those prior to hospitalization (p<0.05). Correlation analysis revealed a positive correlation between the serum concentration of HMGB1 and coronary artery lesion counts and severity as evaluated using the Gensini integral (r=0.525, p<0.01 and r=0.588, p<0.01, respectively), and a negative correlation with left ventricular ejection fraction (r=-0.488, p<0.01) in patients with ACS. Moreover, the serum concentration of TNF-α was positively correlated with that of HMGB1 (r=0.415, p<0.01). The serum concentrations of HMGB1 and TNF-α may be useful indicators to estimate the severity of coronary artery lesions in patients with ACS.

Introduction

Acute Coronary Syndrome (ACS) is characterized by a complex multifactorial pathogenesis, which involves an inflammatory response, immune damage, and the activation of the blood clotting function [1]. Thus far, researchers studying the fundamental mechanism of ACS have suggested that inflammation causes coronary atherosclerotic plaque instability and leads to the activation of endothelial cells, which results in the rupture of plaques and thrombus formation [2,3]. In addition, the progression of thrombus formation is associated with inflammation, and the proinflammatory state appears to increase the risk of coronary artery thrombosis, which suggests that the inflammatory response plays an important role in the onset of ACS [4].

Particular attention has recently been focused on High-Mobility Group Box-1 (HMGB1) protein as a potential biochemical marker, since this protein is responsible for triggering the inflammatory reaction and immune response during tissue damage and infection [5]. HMGB1 can be either passively released from necrotic cells or actively secreted by monocytes or macrophages upon inflammatory stimulation, and acts as a potent mediator [6] that can enhance the release of inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), interleukin 1, and interleukin 6, and thereby induce a harmful inflammatory response [7-10]. In recent years, a growing body of evidence has shown that HMGB1 plays a pivotal role in cardiovascular diseases, including atherosclerosis, myocardial ischemia/reperfusion injury, and ACS [11-14]. Moreover, increased concentrations of serum HMGB1 have been demonstrated in patients with ACS, and a high concentration of HMGB1 was associated with impaired cardiopulmonary function and autonomic dysfunction in previous clinical studies [14-17]. Thus, HMGB1 not only mediates the inflammatory response, but also enhances tissue growth and remodeling, and the activity of these processes may

depend on its concentration [12]. However, the changes in serum HMGB1 and TNF-α concentration in patients with ACS remain unclear.

Therefore, the aim of this study was to measure the serum concentrations of HMGB1 and TNF-α in a group of ACS patients before and after standardized hospitalization. We then delineated the trends of HMGB1 and TNF-α in the ACS group to determine whether correlations exist between HMGB1 concentration, TNF-α concentration, coronary artery lesion counts or severity, and cardiac function.

Materials and Methods

Patients and study design

We prospectively enrolled patients who were admitted to the First Affiliated Hospital of Shihezi University because of ACS (n=60), including those with unstable angina pectoris (UAP) (n=30; age range 42-78 years; mean 59.63 ± 9.97 years) or Acute Myocardial Infarction (AMI) (n=30; age range 40-76 years; mean 54.77 ± 10.09 years). Patients presenting with ACS were treated with primary percutaneous coronary intervention between March 2013 and September 2014. Meanwhile, the patients who did not present with artery lesions on Coronary Angiography (CAG) were regarded as a control group (n=30; age range 38-73 years; mean 54.07 ± 11.07 years). The diagnoses of unstable angina and acute myocardial infarction were consistent with the current guidelines [18,19]. Exclusion criteria included patients with liver and kidney dysfunction, chronic heart failure, malignant arrhythmia, stroke, acute or chronic infectious disease, autoimmune disease, cancer, and trauma. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shihezi University. Written informed consent was obtained from all participants.

Sample collection and biochemical investigation

Peripheral venous blood was drawn from the elbow vein of each patient in the three groups at different time points, as follows: AMI group, prior to emergency coronary intervention and post-standardized hospitalization; UAP group, before and after standardized hospitalization; control group, in the early morning and on an empty stomach. Blood samples were placed in 5 ml containers containing ethylenediamine tetraacetic acid, left standing for 20 min, centrifuged at 3000 rpm for 10 min, and stored at-70°C until further analysis. Serum urea nitrogen, creatinine, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured using standard laboratory techniques and an automatic biochemistry analyser (Olympus, Tokyo, Japan). Serum concentrations of HMGB1 and TNF-α were assessed by enzyme-linked immunosorbent assay according to the instructions of the manufacturer (ELISA Kit for human HMGB1 and TNF-α, USCN Life Science Inc., Wuhan, China).

CAG and Gensini coronary score

All the examined patients underwent CAG, and the results were interpreted by two experienced cardiologists. The severity of coronary artery stenosis was assessed by the Gensini coronary score [20] as follows: a score of 1 was given for 1-24% coronary artery narrowing, a score of 2 for 25-50% narrowing, a score of 4 for 51-75% narrowing, a score of 8 for 76-90% narrowing, a score of 16 for 91-99% narrowing, and a score of 32 for total occlusion. Thenceforth, the score was multiplied by a factor that incorporated the significance of the lesion's localization in the coronary arterial tree. For instance, "5" for the left main coronary artery, "2.5" for the proximal left anterior descending coronary artery (LAD) or left circumflex coronary artery (LCX), "1.5" for the mid-LAD, and "1" for the distal LAD or mid-distal LCX. Finally, we divided the patient cohort into three groups according to their degree of stenosis, as follows: mild stenosis group (a Gensini score of 1-24), moderate stenosis group (a score of 25-49), and severe stenosis group (a score of greater than or equal to 50).

Doppler-echocardiography

Doppler-echocardiography (GE, Fairfield, CT, USA) was performed to examine the related indicators of all patients, including Left Ventricular Ejection Fraction (LVEF), Left Ventricular End-Diastolic Diameter (LVEDD), and Left Ventricular Fractional Shortening (LVFS).

Statistical analysis

Statistical analyses were performed using SPSS, version 22.0 (IBM, Armonk, NY, USA). Categorical variables were given as percentages and compared by the χ^2 test. Continuous variables were presented as mean ± Standard Deviation (SD) and compared by unpaired and paired-sample Student t-tests or one-way analysis of variance for multiple variables, as applicable. The bivariate correlation was assessed by Pearson's test. Differences with $p<0.05$ were considered statistically significant.

Results

Baseline characteristics

A total of 90 patients were included in the study, including 30 patients with AMI, 30 with UAP, and 30 controls. The demographic and clinical characteristics of the patients in each group are shown in Table 1. No statistically significant differences were detected with respect to the baseline variables among the three groups, except for higher rates of diabetes mellitus in the AMI and UAP groups.

Table 1. *Comparison of baseline characteristics among AMI, UAP and control group.*

Variables	AMI group (n=30)	UAP group (n=30)	Control group (n=30)	t or χ²	P

Male (%)	22 (73.3%)	21 (70%)	20 (66.6%)	0.317	0.853
Age (year)	54.77 ± 10.09	59.63 ± 9.97	54.07 ± 11.07	2.555	0.084
BMI (kg/m2)	25.66 ± 2.05	26.07 ± 2.46	25.38 ± 2.63	0.618	0.541
Smoking (%)	22 (73.3%)	19 (63.3%)	18 (60.0%)	1.279	0.527
Hypertension (%)	16 (53.3%)	17 (56.7%)	13 (43.3%)	1.156	0.561
Diabetes (%)	3 (10.0%)	9 (30%)	2 (6.7%)	7.274	0.026
BUN (mmol/l)	5.01 ± 1.37	4.47 ± 1. 45	4.67 ± 0.96	1.408	0.25
CR (mmol/l)	89.20 ± 51.92	76.92 ± 19.04	72.40 ± 12.22	2.121	0.126
FBG (mmol/l)	5.81 ± 2.76	5.71 ± 1.88	4.86 ± 0.98	2.044	0.136
TG (mmol/l)	1.76 ± 1.25	1.72 ± 1.22	1.56 ± 0.81	0.277	0.759
LDL-C (mmol/l)	2.58 ± 0.74	2.41 ± 0.93	2.39 ± 0.78	0.46	0.633
HDL-C (mmol/l)	0.96 ± 0.27	1.02 ± 0.23	1.10 ± 0.30	1.996	0.142
TC (mmol/l)	4.12 ± 1.01	4.15 ± 1.12	4.02 ± 0.92	0.14	0.87

Serum concentrations of HMGB1 and TNF-α

Serum concentrations of HMGB1 (33.22 ± 16.59 ng/ml in the AMI group and 23.40 ± 12.17 ng/ml in the UAP group) and TNF-α (10.68 ± 4.94 pg/ml in the AMI group and 6.37 ± 3.53 pg/ml in the UAP group) in patients with ACS prior to standardized hospitalization were significantly higher than in those of control group (HMGB1: 12.23 ± 2.74 ng/ml; TNF-α: 2.13 ± 1.26 pg/ml) (p<0.01). Compared with those in the AMI group, serum HMGB1 and TNF-α concentration in the UAP group were significantly reduced before treatment (p<0.01, Table 2). The concentrations of HMGB1 (21.67 ± 13.00 ng/ml in the AMI group and 18.71 ± 6.92 ng/ml in the UAP group) and TNF-α (5.28 ± 3.09 pg/ml in the AMI group and 3.71 ± 2.34 pg/ml in the UAP group) in patients with ACS post-standardized hospitalization were lower than prior to hospitalization (p<0.05, Table 3).

Table 2. Comparison of HMGB1, TNF-α level among three groups before the standardized hospitalization ($\bar{x} \pm s$).

Group	n	HMGB1(ng/ml)	TNF-α (pg/ml)
AMI	30	33.22 ± 16.59[a]	10.68 ± 4.94[a]
UAP	30	23.40 ± 12.17[ab]	6.37 ± 3.53[ab]
Control	30	12.23 ± 2.74	2.13 ± 1.26

[a]P<0.01 *vs.* control; [b]P<0.01*vs.* AMI group.

Table 3. Comparison of HMGB1 and TNF-α level between AMI group and UAP group before and after the standardized hospitalization ($\bar{x} \pm s$).

	n	HMGB1 (ng/ml)		TNF-α (pg/ml)	
		Prior treatment	Post treatment	Prior treatment	Post treatment
AMI group	30	33.22 ± 16.59	21.67 ± 13.00[a]	10.68 ± 4.94	6.37 ± 3.53[a]
UAP group	30	23.40 ± 12.17	18.71 ± 6.92[b]	5.28 ± 3.09	3.71 ± 2.34[b]

[a]P<0.01 *vs.* prior treatment; [b]P<0.05 *vs.* prior treatment

Serum concentration of HMGB1 and coronary artery lesions

The serum HMGB1 concentrations in ACS patients with different numbers of coronary artery lesions were as follows: 13.45 ± 4.48 ng/ml for single lesions, 27.39 ± 15.22 ng/ml for double lesions, and 40.79 ± 18.51 ng/ml for multiple lesions (p<0.01, Table 4). Serum HMGB1 concentrations according to the degree of stenosis were 14.91 ± 6.18 ng/ml for mild stenosis, 29.63 ± 21.81 ng/ml for moderate stenosis, and 41.74 ± 10.37 ng/ml for severe stenosis. The differences between groups were statistically significant (p<0.05, Table 5).

Table 4. Changes of HMGB1 levels from different coronary lesion vessels ($\bar{x} \pm s$).

Group	n	HMGB1 (ng/ml)
Single-lesion	12	13.45 ± 4.48[ab]
Double-lesions	22	27.39 ± 15.22
Multi-lesions	26	40.79 ± 18.51[b]

[a]P<0.01 *vs.* multi-lesions; [b]P<0.05 *vs.* double-lesions group.

Table 5. Changes of HMGB1 levels from different stenosis degree of coronary artery ($\bar{x} \pm s$).

Group	n	Gensini score	HMGB1 (ng/ml)
Mild stenosis	18	17.19 ± 5.91	14.91 ± 6.18[ab]
Moderate tenosis	22	36.91 ± 6.82	29.63 ± 21.81
Severe tenosis	20	78.18 ± 22.72	41.74 ± 10.37[b]

[a]P<0.01 *vs.* severe tenosis group; [b]P<0.05 *vs.* moderate tenosis group.

Serum concentration of HMGB1 and echocardiography parameters

Compared with the control group, LVEF and FS in patients with ACS were significantly lower (p<0.01 and p<0.05, respectively), and no significant difference was observed for LVEDD (Table 6).

Table 6. Comparison of echocardiography parameters between AMI group and control group ($\bar{x} \pm s$).

Group	n	LVEF (%)	FS (%)	LVEDD (mm)	F	P
AMI	30	54.00 ± 11.24	62.88 ± 6.17	63.13 ± 5.81	11.652	0
UAP	30	30.43 ± 8.70	34.60 ± 4.31	34.38 ± 4.31	4.305	0.017
Control	30	47.97 ± 7.49	47.00 ± 4.15	46.33 ± 3.54	0.693	0.503

Correlations between serum HMGB1 concentration and physiopathological parameters

Correlation analysis showed that the serum concentration of HMGB1 was positively correlated with coronary artery lesion counts and coronary artery lesions using the Gensini integral (r=0.525, p<0.01 and r=0.588, p<0.01, respectively), but it was negatively correlated with LVEF (r=-0.488, p<0.01) in patients with ACS. Moreover, the serum concentration of TNF-α was positively correlated with that of HMGB1 (r=0.415, p<0.01, Table 7).

Table 7. Correlation of serum HMGB1 levels with relevant parameters in ACS patients (n=60).

	HMGB1 (ng/ml)	
	R	P
Coronary artery lesion vessels	0.525	0.001
Gensini score	0.588	0
LVEF	-0.488	0.003
TNF-α (pg/ml)	0.415	0

Discussion

Recent studies have demonstrated an association between the inflammatory response and coronary artery disease, since an excessive and persistent inflammatory response might have a pivotal role in causing myocardial injuries [4]. Various biochemical markers of inflammation have been identified as predictors of the severity of coronary events [21]. The major aim of the present study was to investigate the correlations between the serum concentration of HMGB1, that of TNF-α, and ACS. It has been reported that HMGB1 is not only actively secreted in response to proinflammatory stimuli, but it is also passively released from necrotic cells upon inflammatory stimulation and functions as a proinflammatory agent [22,23]. A previous study showed that the serum concentrations of HMGB1 were significantly increased in patients with AMI and UAP compared to controls, which indicated that HMGB1 might participate in the formation and development of the atherosclerotic plaque. Such increased HMGB1 concentrations may be closely related to an excessive and persistent inflammatory response, endothelial dysfunction, and atherosclerotic plaque instability [24]. Moreover, Andrassy et al. observed that serum HMGB1 concentrations were elevated in patients with ACS, particularly in those with AMI, and confirmed that the concentration of HMGB1 was correlated with cardiac troponin I and infarction size [14,25]. In agreement with previous studies, we demonstrated here that patients with ACS had an obviously increased concentration of serum HMGB1 prior to standardized hospitalization [24]. In addition, we found that the serum concentration of HMGB1 was positively correlated with coronary artery lesion counts and severity as evaluated using the Gensini integral. A recent study in patients with non-ST-segment elevation ACS found a

positive correlation between the serum concentration of HMGB1 and the degree of the decline of heart function [13]. The group with a significantly higher concentration of HMGB1 also had a significantly reduced LVEF. Hashimoto et al. [13,15] found that the concentration of HMGB1 in the serum can predict the mortality of cardiovascular disease, to a certain extent, and the prognosis of patients with high concentrations of serum HMGB1 was poor considering the deterioration of cardiac function. In this study, we investigated the relationship between the results of ultrasound examination and the concentration of serum HMGB1. The finding that the concentration of serum HMGB1 was negatively correlated with LVEF suggests that measuring the concentration of HMGB1 in serum may provide a reference for the early evaluation of left ventricular systolic function in patients with ACS. ACS, which is a serious type of coronary heart disease, is a clinical syndrome caused by acute myocardial ischemia. According to patient medical history, the features of coronary artery lesions, and the severity of coronary artery stenosis shown by the CAG, patients with indications for surgical treatment after percutaneous coronary intervention should have the occlusion removed or be given stenosis of the coronary artery as soon as possible. This is a key and difficult point in clinical work and needs to be done to restore the blood flow to coronary circulation, prevent or decrease the scope of myocardial necrosis, and protect cardiac function. Percutaneous coronary intervention has been widely used in the clinic as one of the most effective methods for the treatment of coronary revascularization. In this study, ACS patients were treated with 1-3 stents according to the severity of their coronary lesions. By comparing the concentrations of serum HMGB1 at different time points, we found that its mean concentration in patients with ACS was significantly lower post-standardized treatment but still higher than that in the control group, which suggested that HMGB1 might play an important role in the occurrence and development of ACS. When acute myocardial ischemia injury occurs, a high concentration of serum HMGB1 can aggravate the myocardial pathological damage in the early stages of ACS, while it plays an active role in the repair of myocardial muscle at the late stage of acute myocardial ischemia [4-13]. The time and the concentration of HMGB1 at which treatment of patients with coronary heart disease is most appropriate to strengthen the regeneration of the blood vessels, recover heart function, and improve the prognosis needs to be researched and studied further. As a potent proinflammatory cytokine, TNF-α is derived from endothelial cells, foam cells, and macrophages, which are related to coronary atherosclerosis. Animal experimental studies have shown that the expression of the inflammatory cytokine TNF-α in a model of myocardial ischemia reperfusion injury in rats was significantly higher than that in a sham operation group, and it may reduce the occurrence of myocardial ischemia reperfusion injury by blocking the production and inhibiting the activation of TNF-α. Clinical studies have shown that the expression of TNF-α in patients with ACS displayed a gradually increasing trend from 6 h to 24 h after they started to experience chest pains, and the

expression of TNF-α reflected the degree of coronary artery disease, to a certain extent, and possessed a certain value in predicting the severity of disease [25]. Based on the studies mentioned above, we envisaged that the serum concentration of TNF-α in patient with ACS may prove valuable in evaluating the severity of the early stages of the disease. Our study showed that the serum concentrations of TNF-α in the control group, UAP group, and AMI group were elevated before the standard treatment, and the results were consistent with previous studies, which indicated that the concentration of TNF-α may be associated with the severity of coronary lesions [26,27]. The changes of TNF-α concentration in heart disease may be due to the effect of cytokines binding to different receptors at different times. TNF-α exerted a short-term negative effect on muscle strength and increased myocardial tissue damage by binding with TNFR1 at the early stage of acute myocardial ischemia, while it played a protective role in cell by binding with TNFR2 at the late stage of myocardial ischemia [28,29]. In addition, the trend towards a changing concentration of serum TNF-α in patients with ACS before and after a standardized treatment, as found in the present study, may indicate that the serum concentration of TNF-α can to some extent reflect the conditions of coronary artery disease and myocardial ischemia. Effective control of the inflammatory reaction may have some significance for reducing myocardial ischemia injury, but its mechanism requires further study.

In the process of myocardial ischemia, HMGB1 is passively released from necrotic cells and recognized by the immune system, which induces an inflammatory reaction. It maintains or aggravates the inflammatory reaction by combining with its receptors RAGE and TLR4, activating the process of nuclear transcription, inducing the activation of NF-κB, and stimulating the secretion of TNF-α or other inflammatory cytokines. Meanwhile, TNF-α is able to stimulate the production of HMGB1, causing an inflammatory cascade amplification reaction, enlarging the initial inflammatory signal, and aggravating tissue damage. Our results from this study showed that the concentrations of serum HMGB1 and TNF-α in patients with ACS were positively correlated, suggesting that they might mutually contribute to the processes of myocardial ischemia and ACS.

Conclusion

This study found that the concentrations of serum HMGB1 and TNF-α in the UAP and AMI groups, prior to the standard treatment, were significantly higher than those in the control group. Additionally, their concentrations in the UAP and AMI groups after the standard treatment were significantly lower than those in the control group. Taken together, these findings suggested that serum HMGB1 and TNF-α might be involved in the onset and progress of ACS. These changes may reflect the presence of coronary lesions and myocardial ischemia in patients with ACS. The serum concentration of HMGB1 in patients with ACS was positively correlated with the severity of coronary artery stenosis, the Gensini score, and the serum

concentration of TNF-α, and it was negatively correlated with LVEF. Taken together, the findings suggest that HMGB1 and TNF-α may be useful as molecular indicators of the severity of coronary lesions in patients with ACS.

Acknowledgements

Conflict of Interest

All authors have no conflict of interest regarding this paper.

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