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Original Article

Elevated MMP-1 and TIMP-1 are related with acute cerebral infarction patients with diabetes mellitus

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Abstract: Objective: We measured serum matrix metalloproteinase-1 (MMP-1) and tissue inhibitor of metalloproteinases-1 (TIMP-1) level in diabetic patients with acute cerebral infarction (ACI); and their clinical significance in the development of cerebral infarction. Methods: A total of 87 diabetic patients with ACI were recruited successfully as group A; 67 diabetic patients without cerebral infarction (group B), 61 non-diabetic cerebral infarction (NDCI) patients (group C) and 58 healthy cases (group D) were recruited for comparisons. The elbow vein blood was collected in diabetic patients with ACI at the 1st, 3nd and 7th day of their onset; and the blood was collected in other 3 groups at their routine physical examination. The expressions of MMP-1 and TIMP-1 were measured by enzyme-linked immunosorbent assays (ELISA) methods. Results: The expressions of MMP-1 and TIMP-1 in diabetic patients with ACI in the 1st, 3nd and 7th day were obviously higher than diabetic patients without cerebral infarction, non-diabetic cerebral infarction patients and healthy control ($p < 0.05$). For diabetic patients with ACI, the expressions of MMP-1 and TIMP-1 in 3 time points have statistical difference ($p < 0.05$); and the levels of MMP-1 and TIMP-1 gradually increased with the deterioration of the ACI. Conclusions: For diabetic patients with cerebral infarction, the elevated levels of MMP-1, TIMP-1 in serum are positively related with blood glucose levels, and the deterioration of cerebral infarction. The detection of MMP-1 and TIMP-1 in diabetic patients with cerebral infarction might useful for the prevention of early onset of acute cerebral infarction.

Keywords: Diabetes, cerebral infarction, matrix metalloproteinase-1, tissue inhibitor of metalloproteinases-1

Introduction

Cerebrovascular lesions in diabetes is an important fatal factor in diabetes [1, 2]. Research has indicated the attack rate of cerebral infarction in diabetic patients is double to patients without diabetes [3]. The cerebral ischemia could cause expression of matrix metalloproteinases (MMPs), thus promote the degradation of extracellular matrix (ECM) and the open of blood brain barrier after perfusion, finally resulting in cerebral hemorrhage, brain edema and leucocytes infiltration [4, 5]. At least 25 different MMPs have been identified in humans, Pasterkamp indicated a large number of matrix metalloproteinases (MMPs) existed in atherosclerotic plaques, which can lead to plaque rupture and remodeling of extracellular matrix [6]. MMP-1, also known as interstitial collagenase, is highest expressed matrix metalloproteinase in intestinal collagenase, MMP-1 could degrade type I and type V collagen, which are abundantly inside the human body; the degradation of extracellular matrix caused by MMP-1 could promote opening of blood brain barrier after re-perfusion [7, 8]. Currently, compelling studies have demonstrated abnormal expression of MMP-1 is correlated with many diseases, including cardiovascular disease [9], kidney disease [10], coronary artery disease [11] and cerebrovascular disease, etc. [12].

Tissue inhibitor of metalloproteinases (TIMPs) could specifically inhibit the MMPs. As one of TIMPs, TIMP-1 could inhibit MMP-1 expression. Kittaka reported the serum MMP-9 and TIMP-1 levels in infants with human herpesvirus-6 infection were significantly higher in infants

Table 1. Demographic data of the 4 groups' patients

	Diabetic patients with ACI	Diabetic patients without CI	Non-diabetic CI	Healthy control	*P* value
N	87	67	61	58	> 0.05
Male (%)	51 (58.6%)	32 (47.8%)	35 (57.4%)	37 (63.8%)	> 0.05
Age (yr)	59.6 ± 5.2	57.6 ± 5.3	59.7 ± 4.8	61.45 ± 4.6	> 0.05
Age range (yr)	38-72	51-68	52-70	49-73	
FBG (mmol/L)	12.3 ± 1.7$^{**,\#}$	10.6 ± 1.5**	5.1 ± 1.4	5.2 ± 1.6	
HbAlc (%)	10.8 ± 2.6**	9.5 ± 2.1**	5.2 ± 1.7	5.1 ± 1.5	

Note: Abbreviation: FBG: fasting blood glucose; *P* value was analyzed by one-way analysis of variance (ANOVA), following post hoc with Tukey's test. **P < 0.01, compared with Non-diabetic CI and healthy control. $^{\#}$P < 0.05, compared with group of diabetic patients without CI.

with HHV-6 infection than in controls [13]. Current researches also demonstrated MMPs play a detrimental role related to hemorrhagic transformation and severity of an ischemic brain lesion, and lead to the change of TIMP-1 level [14-16]. Few studies focus on the correlation between MMP-1, TIMP-1 and the occurrence of cerebral infarction in patients with diabetes mellitus. In these study, we recruited 4 groups of subjects to test and compare the expression of MMP-1 and TIMP-1 among them: diabetic patients with acute cerebral infarction; diabetic patients without cerebral infarction; non-diabetic cerebral infarction patients and healthy control; And we also compared the levels of MMP-1 and TIMP-1 in acute stage of cerebral infarction patients with diabetes, to explore the clinical significance of MMP-1 and TIMP-1 in diabetic patients with cerebral infarction.

Materials and methods

Subjects and ethnic consideration

All subjects were recruited from October 2010 to December 2012. Following the voluntary principle, 4 groups of subjects aged between 38-73 years were recruited, which were diabetic patients with acute cerebral infarction (ACI) as group A; diabetic patients without cerebral infarction as group B; non-diabetic cerebral infarction patients (group C) and healthy controls (group D) respectively. The patients with myocardial infarction, cerebral hemorrhage, cerebral embolism, infection, tumor, liver and kidney disease were excluded from this study.

The diabetic patients with ACI were confirmed by imaging examination and the condition continued to deteriorate within 7 days of onset; their neural function defect score were evaluated according to the Chinese scale of clinical neurological deficit of stroke patients (China Stroke Scale, CSS) [17]. The diabetes was diagnosed according to the WHO diagnostic criteria in 1999 [18]. Healthy controls were recruited from subjects received routine physical examination in our hospital.

This study was approved by the Institutional Review Board of north china university of science and technology affiliated hospital, and was conducted in accordance with good clinical practice, all applicable regulatory requirements and the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to admission to the study.

Sample collection and testing

3 ml of elbow vein blood was drawn from subjects of each group: diabetic patients with ACI at the 1st, 3nd and 7th day of their onset; non-diabetic cerebral infarction patients within the 24 hour of their onset; blood from only diabetes patients and healthy control were drawn at their physical examination. The enzyme-linked immunosorbent assays (ELISA) methods was used to test levels of MMP-1 and TIMP-1 through ELISA kit (BOSTER Bio Tech Inc., Wuhan, CHN); For diabetes patients, their blood glucose and glycosylated hemoglobin (HbAlc) levels were measured by routine methods.

Statistical analysis

The demographic data in each group were collected. Measurement data were expressed as mean ± standard deviation (SD), and compared with student's t test. The enumeration data data was indicated by the ratio and chi square (χ^2) test was used for comparison. The demographic data among four groups was analyzed by one-way analysis of variance (ANOVA), following post hoc with Tukey's test. The graded

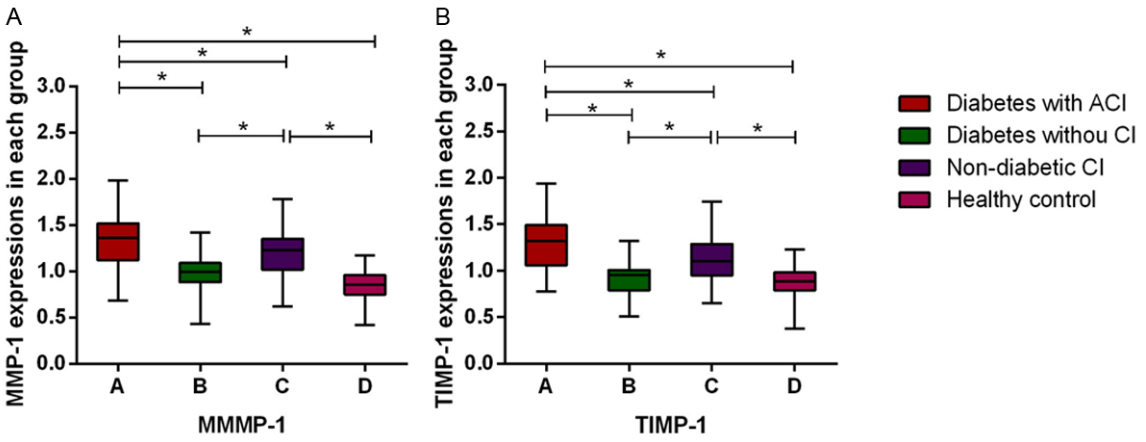

Figure 1. Comparison of MMP-1 and TIMP-1 expression (1st day of onset) in diabetic patients with ACI to diabetic patients without cerebral infarction, non-diabetic cerebral infarction patients and healthy control. *p < 0.05.

measurement data was compared by non-parametric test (Z test). $p < 0.05$ was considered as statistically significant. Pearson correlation was used for correlation between MMP-1 and TIMP-1 expressions and their neurological deficit grade, All the data was analyzed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographic data

From October 2010 to December 2012, a total of 87 diabetic patients with ACI (group A), 67 diabetic patients without cerebral infarction (group B), 61 non-diabetic cerebral infarction (NDCI) patients (group C) and 58 healthy cases (group D) were recruited successfully. Their demographic data were concluded in **Table 1**, the analysis results showed there was no difference in the age and gender distribution between the 4 groups ($p > 0.05$), but FBG (fasting blood glucose) and HbAlc in two diabetic group were significantly higher than healthy group and non-diabetic CI group ($P < 0.01$, **Table 1**).

MMP-1 and TIMP-1 in each group

The measurement dada showed the MMP-1 and TIMP-1 (1st day of onset) in diabetic patients with ACI were significantly higher than diabetic patients without cerebral infarction, non-diabetic cerebral infarction patients and healthy control with statistical difference when compared with other 3 groups ($t = 3.09$ and 11.85 respectively, p all < 0.05, **Figure 1**). In addition, results showed the MMP-1 and TIMP-1 expression in non-diabetic patients with cerebral infarction was also statistically higher than diabetes patient and healthy control ($p < 0.05$). In addition, the ROC curve analysis (**Figure 2**) of MMP-1 and TIMP-1 in diabetic patients with ACI and non-diabetic patients with cerebral infarction (CI) showed the ROC curve area of MMP-1 was 0.6526 with 95% confidence interval (CI) 0.5644 to 0.7408 ($p = 0.001612$); the ROC curve area of TIMP-1 was 0.6935 with 95% confidence interval (CI) 0.6093 to 0.7777 ($p < 0.0001$). These results showed the MMP-1 and TIMP-1 have better diagnostic significance while their diagnosis accuracy were relative low (AUC 0.5~0.7).

MMP-1 and TIMP-1 elevated with the progression of acute cerebral infarction

We also compared the expressions of MMP-1 and TIMP-1 in diabetes patients with acute cerebral infarction at the 1st, 3nd and 7th day from their onset when their condition continued to deteriorate within 7 days. Results showed expressions of MMP-1 and TIMP-1 increased with the deterioration of the patients, The expressions have statistical difference at day 3 when compared with day 1 and day 7 ($p < 0.05$, **Table 2**).

Expressions of MMP-1 and TIMP-1 are positively correlated with the neurological deficit grade

In addition, we also analyzed the neurological deficit degree (evaluated by China Stroke Scale (CSS)), and the expressions of MMP-1 and TIMP-1. The correlation analysis (**Table 3**)

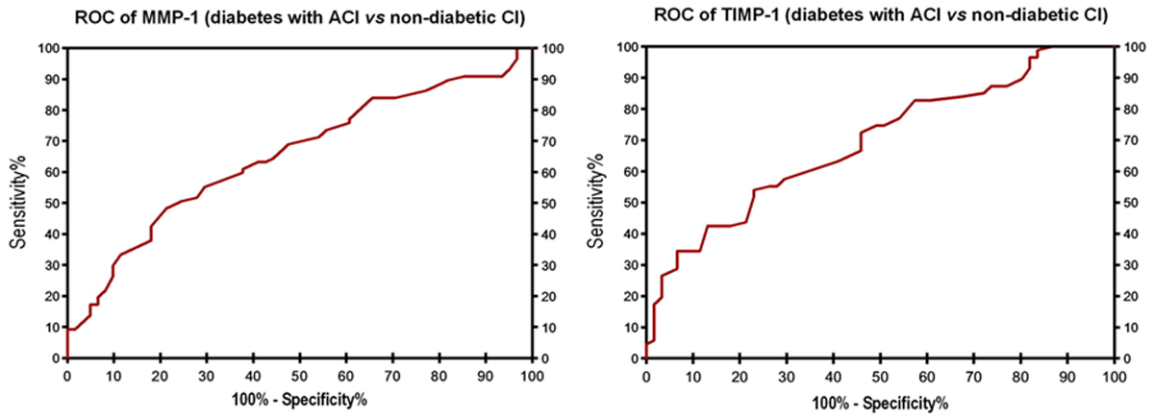

Figure 2. The ROC curve of MMP-1 and TIMP-1 (diabetes with ACI vs non-diabetic CI), and AUC (Area Under Curve) was calculated.

Table 2. MMP-1 and TIMP-1 expressions in in diabetes patients with acute cerebral infarction (mean ± SD, μg/L)

Time point	MMP-1	TIMP-1
Day 1	1.325 ± 0.247	1.296 ± 0.236
Day 3	1.642 ± 0.338	1.605 ± 0.341
Day 7	1.781 ± 0.465	1.820 ± 0.426

showed CSS score was moderately correlated with expressions of MMP-1 and TIMP-1 ($r = 0.417$, $r = 0.440$, both $p < 0.05$, respectively). The results in a certain extent demonstrate that the higher the expressions of MMP-1 and TIMP-1 are, the more neurological deficit is.

Discussion

In a healthy human body, the formation and degradation of extracellular matrix (ECM) exist in dynamic equilibrium. As structural components of the vessel wall, ECM plays important role in cerebral infarction [19]. Diabetes induced metabolic abnormalities could change the structure and function of basement membrane, thus lead to the abnormal degradation and regeneration of vascular basement membrane [20]. MMPs and TIMPs are the important enzymes involved in ECM metabolism; MMPs is a Zn^{2+} dependent protease family with the main function of degradation and remodeling of ECM. As the highest expressed MMPs, MMP-1 could degrade the intima and atherosclerotic plaque and damage the blood brain barrier. The TIMPs are MMPs specific tissue inhibitor, through binding the Zn^{2+} in catalytic center of MMPs, TIMP-1 can prevent the catalytic activity of MMPs [21].

The normal expressed MMPs in human body is involved in many physiological and pathological processes: MMPs could promote the wound healing, angiogenesis and development of nerve cells [22]. MMPs are widely existed in the endothelial, astrocytes and microglia cells of the brain; Napoli indicated the increased MMPs expression in carotid artery atherosclerotic plaque is the main pathological features of acute cerebral infarction [23]. Recent research on acute cerebral infarction also indicated the reperfusion injury of cerebral ischemia or ischemia activated MMPs to destroy the matrix and damage the blood-brain barrier, causing brain edema or cerebral hemorrhage, and promoting the acute cerebral infarction [24].

The HbAlc is a product of non-enzymatic protein glycation produced by hemoglobin and glucose in red blood cells irreversibly, HbAlc represents the blood glucose level 6 to 8 weeks before the testing. Maintained a high blood glucose level in patient can make non-enzymatic glycation and advanced glycation of complex protein accumulated rapidly, the toxic effects of the products on the artery wall accelerate the development of atherosclerosis. Peeters et al [25] indicated that plasma levels of matrix metalloproteinase-2, -3, -10, and tissue inhibitor of metalloproteinase-1 are associated with vascular complications in patients with type 1 diabetes; Zhang et al [26] indicated the Matrix metalloproteinase 9 gene promoter (rs 3918-242) mutation reduces the risk of diabetic

Table 3. Correlation analysis between expressions of MMP-1, TIMP-1 and CSS score in diabetes patients with acute cerebral infarction

N = 87		MMP-1	TIMP-1
CSS score	22.13 ± 10.35	1.66 ± 0.48	1.64 ± 0.46
r value		0.417	0.440
P value		0.000	0.000

microvascular complications. The present study shows that the MMP-1 and TIMP-1 expressed abnormally in diabetes patients. These results are consistent with other domestic research in China [27, 28].

TIMP-1 is a natural inhibitor of MMPs, TIMP-1 could inhibit the activity of most MMPs; for vulnerable atherosclerotic plaques, the elevated secretion of several MMPs could cause the corresponding increase of TIMP-1 [29]. Carrell indicated the arteriosclerosis injury could be divided into two categories: (1) the increased number of collagen on vascular wall resulting in the narrowing of the vessel lumen; (2) appearance of aneurysm cause of narrow of lumen volume and lumen rupture. Carrell's study showed that increased MMP-1 and TIMP-1 appeared in the two kinds of damaged vessel wall both [30], which demonstrated the MMP-1 has significant relationship with atherosclerosis. After the onset of cerebral infarction, cerebral blood flow and perfusion pressure decreased rapidly, the varying degrees of reperfusion injury of brain ischemia and ischemia occur, and the expression of MMP-1 and TIMP-1 varied at different time points in patients with cerebral infarction [31].

In this study, the MMP-1 and TIMP-1 in diabetic patients with ACI were significantly higher than other group; the expressions of MMP-1 and TIMP-1 increased with the deterioration of the acute cerebral infarction; and the more severe the deficit of nerve function in patients, the higher the MMP-1 and TIMP-1 expressed. This suggests that MMP-1 plays an important role in the process of destruction of the ECM, and its expression significantly increased in the blood of patients with acute cerebral infarction [32]. It is cannot be ignored that the accuracy of MMP-1 and TIMP-1 in distinguishing in diabetes with acute cerebral infarction and non-diabetic cerebral infarction is not very high, which means that the actual diagnosis of diabetes with acute cerebral infarction in clinical requires a combination of other indexes. With the increasing of MMP-1 expression, TIMP-1 level increased to inhibit MMP-1, thus to alleviate cerebral ischemia and ischemia reperfusion injury [33]. Our results also showed the correlation between MMP-1, TIMP-1 and the degree of neurological defects is strong, which means them could be used to evaluate the degree of acute infarction injury of diabetic patients in clinical practice.

In conclusion, the serum level of MMP-1 and TIMP-1 increased in diabetes patients with acute cerebral infarction; and the expression of MMP-1 and TIMP-1 are related with the blood glucose levels; MMP-1 and TIMP-1 have important roles in the development of cerebral infarction in diabetic patients. They might have certain clinical significance in the early prevention of acute cerebral infarction disease.

Disclosure of conflict of interest

None.

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