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Determination of serum tissue kallikrein levels after traumatic brain injury

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ABSTRACT

Background: Tissue kallikrein (TK) plays an important role in the kallikrein-kinin system. Its protective role has been demonstrated in traumatic brain injury (TBI). We attempted to determine relationship between serum TK levels and trauma severity in addition to clinical outcome in TBI.

Methods: We recruited 112 patients with severe TBI (Glasgow coma scale score < 9) and 112 controls. We configured 2 multivariate models to assess the relationship between serum TK levels and 30-day death. Its prognostic predictive ability was analyzed under receiver operating characteristic curve.

Results: TK levels were significantly lower in patients than in controls (median 0.148 mg/l, the upper - lower quartiles 0.121–0.185 vs. median 0.258 mg/l, the upper - lower quartiles 0.207–0.342, $P < 0.001$). TK levels were closely and positively correlated with Glasgow coma scale score ($r = 0.550$). TK levels < 0.148 mg/l independently predicted 30-day mortality with odds ratio value of 4.752 (95% confidence interval (CI), 1.166–19.367) and 30-day overall survival with hazard ratio value of 3.698 (95% CI, 1.026–13.333). TK levels significantly discriminated 30-day mortality with area under curve of 0.822 (95% CI, 0.738–0.887).

Conclusions: Serum TK can represent a potential predictor of clinical outcome in TBI patients.

1. Introduction

Traumatic brain injury (TBI), especially severe TBI (sTBI), is a very important traumatic form, and accounts for one-third of all injury-related deaths [1–3].The adverse prognosis of TBI is mainly attributed to the lack of therapies available to lessen the effects of TBI [4–6]. To improve TBI prognosis, understanding deeply the pathophysiological mechanisms of TBI is crucial. The kallikrein-kinin system (KKS) has been considered as an inflammatory response system, which influences the biological systems and possesses multiple pleiotropic functions [7–9]. KKS have key roles in vascular permeability and inflammation as well as thrombosis and blood coagulation [10–13]. Tissue kallikrein (TK), a subgroup of serine proteinases, is an important component of the KKS, which processes low molecular weight kininogen to release kinin peptide, in turn activating bradykinin B1 and B2 receptors and triggering a host of biological effects [14]. It has been revealed that TK can regulate blood pressure, contract and relax smooth muscle, stimulate vascular cell growth, improve vascular permeability, inactivate inflammatory cascades, maintain electrolyte balance, and ameliorate pain [15–17]. Of note, TK could exert neuroprotective effects in oxygen-glucose-deprived cells and in the ischemic brain [18–20]. Interestingly, lower circulating TK concentrations was related to incident and recurrence of stroke [21]. Moreover, elevated TK concentrations were independently associated with favorable outcome in ischemic stroke [22]. The accumulating evidence shows that KKS play key roles in TBI [23–27].It is postulated that circulating TK concentrations might be a potential prognostic biomarker in TBI.

2. Materials and methods

2.1. Study population

In this prospective, observational study, we collected isolated sTBI adult patients (≥18 y) admitted within the first 6 h after TBI at our hospital from February 2015 and February 2018. sTBI was defined as Glasgow coma scale (GCS) score < 9 points, when patients were not under the influence of pharmacologic agents or alcohol. Isolated TBI was defined as injury severity score ≤ 9 points in non-cranial aspects. Alternatively, those patients were removed if they had surgery or trauma within recent 4 weeks, other previous or coexisting neurological

Abbreviations: GCS, Glasgow coma scale; HR, hazard ratio; OR, odds ratio; ROC, receiver operating characteristic; sTBI, severe traumatic brain injury; TK, Tissue kallikrein; KKS, kallikrein-kinin system

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diseases (like ischemic stroke and intracerebral hemorrhage), use of antiplatelet, anticoagulant or immunosuppressive medication, chronic infections at study enrollment, infection within recent 4 weeks or severe diseases in other systems or organs (e.g., uremia, liver cirrhosis, malignancy, chronic heart disease and chronic lung disease).A group of healthy volunteers were recruited as the controls. Ethics approval for the collection of samples was obtained from the ethics committee at our hospital. The written informed consent for participation was acquired from the relatives of participants.

2.2. Assessment

Demographic data including age and gender were collected at the initial stage of the clinical study. We also recorded time from trauma to admission. Traumatic causes were classified into automobile/motorcycle, fall/jump and others. Meanwhile, pupillary reactivity was observed. Trauma severity was determined using GCS scores in each patient. At admission, all patients had their computerized tomography examination for head and the radiological parameters, such as abnormal cisterns, midline shift and subarachnoid hemorrhage were recorded too. Clinical outcome was assessed utilizing 30-day death.

2.3. Immune analysis

Peripheral venous blood was acquired from the patients at admission and from controls at study entrance. Blood samples were collected by standard venipuncture through a vein in the antecubital fossa into one serum separator tube. All samples were centrifuged, aliquoted, and stored at −80 °C until tested. Serum TK concentrations were gauged using a double antibody sandwich biotin-avidin enzyme-linked immunosorbent assay kit according to the previously described method [21].

2.4. Statistical methods

Statistical analyses were performed using SPSS software, ver 20.0. A $p < 0.05$ was considered to be statistically significant. Continuous variables were summarized as median (the upper - lower quartiles). A Mann-Whitney *U* test was done to determine intergroup differences of continuous variables. Categorical variables were reported as counts (percentage) and their comparisons were carried out using χ^2 test or Fisher exact test. Associations between variables were reported by Spearman's rank correlation coefficient. Kaplan–Meier method was used to estimate 30-day overall survival. Survival time was compared via the log-rank test. The multivariate Cox's proportional hazard model and binary Logistic regression model were the two multivariate models configured to identify independent factors associated with 30-day overall survival and mortality respectively. Receiver operating characteristic (ROC) curve was constructed to evaluate the prognostic value.

3. Results

3.1. Subject characteristics

During the study period, we at first assessed 142 sTBI patients according to selection criteria. And then, 30 patients were removed because they had surgery or trauma within recent 4 weeks (3 cases), other previous or coexisting neurological diseases (7 cases), use of antiplatelet, anticoagulant or immunosuppressive medication (6 cases), chronic infections at study enrollment (4 cases), infection within recent 4 weeks (3 cases) or severe diseases in other systems or organs (7 cases). At last, we recruited 112 healthy controls and 112 patients with sTBI, who had similar age and percentage of gender. TBI patients were aged at the median value of 44 years (range, 18–76 years; the upper - lower quartiles, 31–57 years). The male/female ratio was 1.6 (68/44). Trauma was caused by automobile/motorcycle (50 patients, 44.6%), fall/jump (42 patients, 37.5%) and others (20 patients, 17.9%). The patients were admitted at the median value of 2.0 h post-traumatically (range, 0.9 to 6.0 h; the upper - lower quartiles, 1.7–2.9 h). GCS score ranged from 3 to 8 (median, 5; the upper - lower quartiles, 4–7). Admission unreactive pupils were revealed in a total of 47 patients (42.0%). Initial head computerized tomography scan showed that 50 patients (44.7%) had abnormal cisterns; fifty-seven patients (50.9%), midline shift > 5 mm;67 patients (59.8%), traumatic subarachnoid hemorrhage. A total of 63 patients (56.3%) underwent surgery in the first 24 h. Via noninvasive blood pressure measurement, systolic arterial pressure ranged from70 to 176 mmHg (median, 122 mmHg; the upper - lower quartiles, 98–145 mmHg); diastolic arterial pressure, from 40 to 102 mmHg (median, 71 mmHg; the upper - lower quartiles, 57–83 mmHg); mean arterial pressure, from 50 to 123 mmHg (median, 89 mmHg; the upper - lower quartiles, 70–101 mmHg). In the study, we detected biochemical variables as follows: serum C-reactive protein concentrations (range,7.7 to 24.3 mg/l; median, 13.6 mg/l; the upper - lower quartiles, 11.8–16.5 mg/l), blood glucose concentrations (range, 2.2 to 20.5 mmol/l; median, 10.5 mmol/l; the upper - lower quartiles, 8.7–12.2 mmol/l), blood white blood cell count (range, 4.0 to 14.7×10^9/l; median, 6.7×10^9/l; the upper - lower quartiles, 5.0–9.6 $\times 10^9$/l) and blood platelet count (range,76 to 256 $\times 10^9$/l; median, 140 $\times 10^9$/l; the upper - lower quartiles, 129–181 $\times 10^9$/l).

3.2. Serum TK concentrations and other variables

In Fig. 1, serum TK concentrations were substantially lower in TBI patients than in healthy controls. In Fig. 2, when GCS score was identified as a categorical variable, serum TK concentrations were significantly elevated with increasing GCS score; while GCS score was considered as a continuous variable, serum TK concentrations were intimately and positively GCS score.

3.3. Thirty-day mortality analysis

Within 30 days after TBI, 26 patients (23.2%, 26/112) were deceased. Serum TK concentrations ranged from 0.032 to 0.194 mg/l (median, 0.111 mg/l; the upper - lower quartiles, 0.066–0.138 mg/l) in the dead. Serum TK concentrations ranged from 0.081 to 0.240 mg/l (median, 0.163 mg/l; the upper - lower quartiles, 0.135–0.200 mg/l) in the alive. The dead had substantially lower serum TK concentrations than the alive ($P < 0.001$). Table 1 shows that the dead exhibited lower GCS scores, older age, a higher proportion of unreactive pupils, abnormal cisterns, midline shift > 5 mm and traumatic subarachnoid hemorrhage, higher blood glucose concentrations, higher serum concentrations of C-reactive protein, higher blood white blood cell counts and a higher percentage of serum TK concentrations < 0.148 mg/l

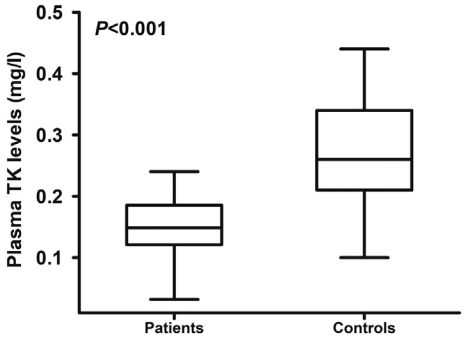

Fig. 1. Difference in terms of serum tissue kallikrein concentrations between healthy controls and patients with severe traumatic brain injury. Graph shows that serum tissue kallikrein concentrations were significantly lower in traumatic brain injury patients, as compared to healthy controls. TK denotes tissue kallikrein.

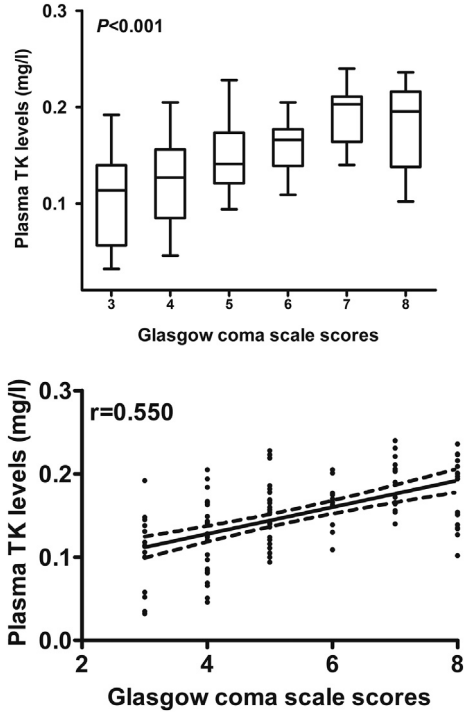

Fig. 2. Relationship between serum tissue kallikrein concentrations and trauma severity reflected by Glasgow coma scale scores among patients with traumatic brain injury. Graph shows that there was an intimate and positive correlation of serum tissue kallikrein concentrations with Glasgow coma scale scores among traumatic brain injury patients. TK denotes tissue kallikrein.

Table 1
Difference in clinical, radiological and biochemical data by 30-day death in 112 patients with traumatic brain injury.

	The dead (n = 26)	The alive (n = 86)	P value
Gender (Male/Female)	14/12	54/32	NS
Age (y)	56 (38–60)	41 (25–54)	0.003
Mechanisms of injury			NS
Automobile/motorcycle	10	40	
Fall/jump	8	34	
Others	8	12	
Glasgow coma scale scores	4 (3–4)	6 (5–7)	< 0.001
Unreactive pupils	23 (88.5%)	24 (27.9%)	< 0.001
Abnormal cisterns	19 (73.1%)	31 (36.1%)	0.001
Midline shift above 5 mm	21 (80.8%)	36 (41.9%)	0.001
Traumatic subarachnoid hemorrhage	23 (88.5%)	44 (51.2%)	0.001
Surgery in the first 24 h	16 (61.5%)	47 (54.7%)	NS
Time from trauma to admission (h)	2.0 (1.5–2.5)	2.0 (1.9–3.0)	NS
Time from trauma to blood-sampling (h)	3.0 (2.8–4.0)	3.6 (2.9–5.0)	NS
Systolic arterial pressure (mmHg)	126 (98–150)	121 (97–139)	NS
Diastolic arterial pressure (mmHg)	71 (56–81)	70 (57–84)	NS
Mean arterial pressure (mmHg)	90 (67–101)	88 (71–101)	NS
Serum tissue kallikrein < 0.148 mg/l	23 (88.5%)	33 (38.4%)	< 0.001
Serum C-reactive protein (mg/l)	16.2 (12.1–20.3)	13.1 (11.8–16.0)	0.039
Blood glucose (mmol/l)	11.9 (9.2–16.4)	10.2 (8.6–11.8)	0.022
Blood platelet count ($\times 10^9$/l)	138 (96–183)	143 (130–178)	NS
Blood white blood cell count ($\times 10^9$/l)	9.9 (5.0–12.5)	6.7 (5.0–8.7)	0.042

Intergroup comparison was done using Mann-Whitney U test, χ^2 test or Fisher exact test as appropriate.

Table 2
The factors related to 30-day mortality after traumatic brain injury.

	Odds ratio	95% confidence interval	P value
Gender (Male/Female)	0.691	0.285–1.677	NS
Age (y)	1.043	1.013–1.073	0.004
Mechanisms of injury			
Automobile/motorcycle	Reference		
Fall/jump	0.375	0.121–1.163	NS
Others	0.353	0.108–1.149	NS
Glasgow coma scale scores	0.198	0.095–0.413	< 0.001
Unreactive pupils	19.806	5.440–72.101	< 0.001
Abnormal cisterns	4.816	1.822–12.729	0.002
Midline shift > 5 mm	5.833	2.010–16.926	0.001
Traumatic subarachnoid hemorrhage	7.318	2.044–26.196	0.002
Surgery in the first 24 h	1.328	0.541–3.255	NS
Time from trauma to admission (h)	0.668	0.421–1.061	NS
Time from trauma to blood-sampling (h)	0.749	0.527–1.064	NS
Systolic arterial pressure (mmHg)	1.005	0.990–1.021	NS
Diastolic arterial pressure (mmHg)	0.995	0.969–1.021	NS
Mean arterial pressure (mmHg)	1.001	0.979–1.023	NS
Serum C-reactive protein (mg/l)	1.146	1.022–1.286	0.020
Serum tissue kallikrein < 0.148 mg/l	12.313	3.426–44.251	< 0.001
Blood glucose (mmol/l)	1.164	1.034–1.310	0.012
Blood platelet count ($\times 10^9$/l)	0.992	0.981–1.004	NS
Blood white blood cell count ($\times 10^9$/l)	1.262	1.075–1.482	0.004

Univariate binary regression analysis was conducted to estimate the odds ratio and 95% confidence interval values associated with 30-day mortality.

(median value). Also, in the univariable binary logistic regression model, we calculated their values of OR and 95% CI in Table 2. Moreover, when the preceding variables were included into the multivariable binary logistic regression model, serum TK concentrations < 0.148 mg/l (odds ratio (OR) = 4.752, 95% confidence interval (CI) = 1.166–19.367, P = 0.030) and GCS score (OR = 0.251, 95% CI = 0.115–0.548, P = 0.001) retained as the two independent predictors for 30-day mortality after TBI.

In order to investigate whether serum TK concentrations could significantly distinguish posttraumatic thirty-day death, a ROC curve was configured. Subsequently, automatically yielded AUC was 0.822 (95% CI = 0.738–0.887, P < 0.001, Fig. 3). In addition, the selected optimal cutoff value was 0.148 mg/l, which generated the highest Youden J index (0.501) and predicted 30-day mortality with a sensitivity of 88.5% and a specificity of 61.6%.

3.4. Thirty-day survival analysis

During 30-day follow-up, the mean overall survival time was 25.2 days (95%CI, 23.2–26.9 days) among all patients. Alternatively, serum TK concentrations were dichotomized in accordance with its median value (0.148 mg/l). In Fig. 3, patients with serum TK concentrations < 0.148 mg/l had significantly shorter 30-day overall survival time than the remainders (mean, 21.5 days; 95%CI, 18.6–24.4 days vs. mean, 28.8 days; 95%CI, 27.4–29.9 days; P < 0.001).

In Table 3, the factors associated with 30-day shorter overall survival time were as follows: GCS scores, age, unreactive pupils, abnormal cisterns, midline shift > 5 mm, traumatic subarachnoid hemorrhage, blood glucose concentrations, serum C-reactive protein concentrations, blood white blood cell count and serum TK concentrations < 0.148 mg/l. Moreover, the aforementioned significant variables were entered into a multivariate model and subsequently, it was found that GCS scores

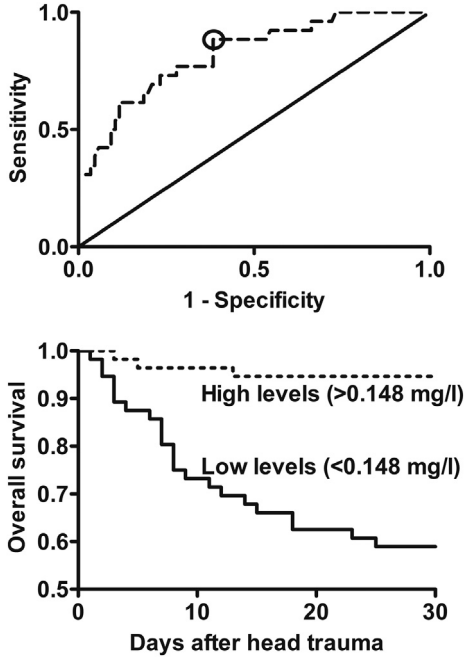

Fig. 3. Relation of serum tissue kallikrein concentrations to thirty-day death after severe traumatic brain injury. The receiver operating characteristic curve was configured to investigate the discriminatory ability of serum tissue kallikrein concentrations for patients at risk of 30-day death after traumatic brain injury. The circle in this graph means a point corresponding to an optimal cutoff value of serum tissue kallikrein concentrations (0.148 mg/l), which predicted 30-day mortality with a sensitivity of 88.5% and a specificity of 61.6%. Survival curve was configured to compare difference in terms of 30-day overall survival time. Patients with serum tissue kallikrein concentrations < 0.148 mg/l had markedly shorter 30-day overall survival time than those with serum tissue kallikrein concentrations > 0.148 mg/l.

Table 3
The parameters related to 30-day overall survival following traumatic brain injury.

	Hazard ratio	95% confidence interval	*P* value
Gender (Male/Female)	0.713	0.330–1.541	NS
Age (y)	1.034	1.010–1.059	0.006
Mechanisms of injury			
Automobile/motorcycle	Reference		
Fall/jump	0.442	0.174–1.120	NS
Others	0.443	0.166–1.180	NS
Glasgow coma scale scores	0.321	0.204–0.507	< 0.001
Unreactive pupils	13.649	4.090–45.546	< 0.001
Abnormal cisterns	4.063	1.706–9.677	0.002
Midline shift > 5 mm	4.821	1.816–12.798	0.002
Traumatic subarachnoid hemorrhage	6.238	1.871–20.795	0.003
Surgery in the first 24 h	1.275	0.578–2.809	NS
Time from trauma to admission (h)	0.709	0.469–1.072	NS
Time from trauma to blood-sampling (h)	0.785	0.575–1.070	NS
Systolic arterial pressure (mmHg)	1.005	0.991–1.018	NS
Diastolic arterial pressure (mmHg)	0.996	0.974–1.019	NS
Mean arterial pressure (mmHg)	1.001	0.982–1.020	NS
Serum C-reactive protein (mg/l)	1.129	1.029–1.238	0.010
Serum tissue kallikrein < 0.148 mg/l	9.269	2.788–30.994	< 0.001
Blood glucose levels (mmol/l)	1.146	1.039–1.265	0.007
Blood platelet count ($\times 10^9$/l)	0.993	0.983–1.004	NS
Blood white blood cell count ($\times 10^9$/l)	1.248	1.086–1.434	0.002

Univariate Cox's proportional hazard analysis was conducted to estimate the hazard ratio and 95% confidence interval values associated with 30-day overall survival.

and serum TK concentrations < 0.148 mg/l independently predicted 30-day overall survival with hazard ratio (HR) values of 0.378 (95% CI = 0. 234–0.611, $P = 0.001$) and 3.698 (95% CI = 1.026–13.333, $P = 0.046$) respectively.

4. Discussion

In this prospective, observational study, we found, for the first time, that patients with sTBI have markedly decreased serum TK concentrations. Moreover, serum TK concentrations were highly and positively correlated with GCS scores. Further analysis showed that serum TK concentrations in the dead patients within 30 days after TBI were significantly lower than in the alive patients. Using 2 multivariate models, we found serum TK concentrations remained independently associated with 30-day mortality and overall survival. It is intriguing that serum TK concentrations exhibited a high prognostic ability under ROC curve. These data suggest that TK may be a strong and independent prognostic biomarker for TBI in the Chinese population.

A previous study reported that mean values of plasma TK concentrations of stroke patients and controls were 0.163 and 0.252 mg/l respectively [21].Our study found that their median values were 0.148 and 0.258 mg/l respectively. Thus, those data were consistent. In line with the previous results in other study regarding ischemic stroke and hemorrhagic stroke [21], our study also revealed that serum TK concentrations were substantially lower in TBI patients than in healthy controls. TK protected rat hippocampal CA1 neurons against cerebral ischemia/reperfusion-induced injury, ameliorated cerebral vasospasm in a rabbit model of subarachnoid hemorrhage, protected against ischemic stroke by suppressing inflammatory reaction in rats and mediated brain hemorrhage and edema caused by tissue plasminogen activator therapy in mice after stroke [18–20,28].Taken together, TK should be neuroprotective. Based on our data in human sTBI, it is assumed that TK might be an endogenous protective factor against traumatized brain injury.

The value of TK in clinical practice has been evaluated in several studies [21,22]. However, the association between TK and extent of brain injury remains unclear. It is the first series to assess the relationship between serum TK concentrations and trauma severity in a group of sTBI patients. In the current study, GCS scores were considered as a continuous or categorical variable. Statistical analysis showed that serum TK concentrations were strongly, positively correlated with GCS scores, indicating that serum TK concentrations might facilitate the assessment of trauma severity after sTBI.

A previous study has determined that higher baseline TK was independently associated with a favorable functional outcome and low mortality rate at 90 days after acute ischemic stroke [22]. However, there is a paucity of data available regarding the association of serum TK concentrations with 30-day prognosis in sTBI. Our study found that serum TK concentrations significantly predicted human 30-day mortality after TBI with high discriminatory capability in terms of AUC. In order to confirm the independent relation of serum TK concentrations to 30-day death, we configured 2 multivariate models (namely, Cox's proportional hazard model and binary Logistic regression model). It was verified that serum TK concentrations, identified as a categorical variable, were independently associated with thirty-day mortality and overall survival. Overall, serum TB might represent a promising biomarker for predicting short-term death after TBI.

5. Conclusions

Our study confirmed that decreased serum TK concentrations at admission, in close and inverse correlation with trauma severity, were independently associated with the high risk of 30-daydeath after TBI, indicating serum TK might serve as a useful prognostic marker for TBI.

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