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High plasma adiponectin levels in patients with severe traumatic brain injury

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ABSTRACT

Background: Adiponectin plays an important role in the regulation of tissue inflammation. There is a paucity of data on circulating plasma adiponectin concentrations in human traumatic brain injury. This study is designed to investigate the potential associations between plasma adiponectin levels and clinical outcomes after traumatic brain injury.
Methods: Plasma adiponectin levels of 86 patients with severe traumatic brain injury and 86 healthy subjects were determined. Clinical outcomes included in-hospital mortality, 6-month mortality and 6-month unfavorable outcome (Glasgow Outcome Scale score of 1–3).
Results: Plasma adiponectin levels were significantly higher in patients compared to controls (20.5 ± 5.9 vs. 7.7 ± 2.0 μg/ml; $P < 0.001$) and emerged as an independent predictor of in-hospital mortality [odds ratio (OR), 1.318; 95% confidence interval (CI), 1.049–1.629; $P = 0.008$], 6-month mortality (OR, 1.328; 95% CI, 1.082–1.657; $P = 0.007$) and 6-month unfavorable outcome (OR, 1.240; 95% CI, 1.066–1.443; $P = 0.005$) in a multivariate analysis. For predicting these clinical outcomes, areas under receiver operating characteristic curve of plasma adiponectin level were similar to those of Glasgow Coma scale scores (all $P > 0.05$). However, adiponectin did not improve predictive values of Glasgow Coma scale scores (all $P > 0.05$).
Conclusion: Plasma adiponectin level may represent a novel biomarker for predicting clinical outcomes of traumatic brain injury.

1. Introduction

Adiponectin is a 30-kDa protein synthesized predominantly by white adipose [1], which has insulin-sensitizing, antiatherogenic, and anti-inflammatory properties [2]. Adiponectin plays a role not only in chronic diseases, such as metabolic syndrome and atherosclerosis [3], but also in several acute illnesses [4]. Some evidences revealed that hyperadiponectinemia is associated with liver cirrhosis, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus, all of which are conditions predisposed to wasting [5–8]. Further evidence has shown that hypoadiponectinemia is associated with atherosclerotic cardiovascular events such as myocardial infarction and brain infarction [9–12]. In animal models of ischemia–reperfusion [13] and traumatic brain injury [14], adiponectin level in peripheral blood decreased significantly during the early phase. Nevertheless, high level of plasma adiponectin in acute ischemic or hemorrhagic stroke patients is associated with stroke mortality [15,16]. However, at present there is a paucity of data available on circulating plasma adiponectin concentrations in patients with traumatic brain injury (TBI). The present study was designed to observe changes in plasma adiponectin levels of TBI patients and also assess its association with the clinical outcomes in a group of TBI patients.

2. Subjects and methods

2.1. Study population

Our study included 86 patients who presented with isolated head trauma and postresuscitation Glasgow Coma Scale (GCS) score of ≤8 Shengzhou People's Hospital from January 2010 to July 2012. This study had excluded patients <18 y, those with admission time >6 h since trauma, those with existing previous head trauma, neurological disease, use of antiplatelet or anticoagulant medication, or presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart or lung disease, diabetes mellitus and hypertension. A control group consisted of 86 age- and gender- matched healthy subjects. This study was performed in accordance with the ethical standards of the responsible committee on human experimentation in Shengzhou People's Hospital. Written informed consent was obtained from the patients or someone responsible for them.

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2.2. Assessment

The severity of the TBI was assessed with use of the postresuscitation GCS. Neurology deterioration was defined as occurring in patients who manifested clinically identified episodes of one or more of the following: 1) a spontaneous decrease in GCS motor scores of 2 points or more from the previous examination; 2) a further loss of papillary reactivity; 3) development of papillary asymmetry greater than 1 mm; or 4) deterioration in neurological status sufficient to warrant immediate medical or surgical intervention [17]. Brain computerized tomography (CT) was performed according to standard techniques. Investigators who read them were blinded to clinical information. CT classification was performed using Traumatic Coma Data Bank criteria on initial postresuscitation CT scan according to the method of Marshall et al. [18]. Abnormal cisterns, midline shift >5 mm and presence of traumatic subarachnoid hemorrhage (SAH) on initial CT scan were also recorded.

2.3. End points

Participants were followed up until death or completion of 6 months after trauma. The clinical outcomes included in-hospital mortality, 6-month mortality and 6-month unfavorable outcome. Unfavorable outcome was defined as Glasgow outcome scale score of 1–3 [19]. For follow-up, structure telephone interviews were performed by one doctor who was blinded to clinical information and adiponectin levels.

2.4. Immunoassay methods

Blood samples for adiponectin assessment were collected at admission for patients, and at study entry for healthy individuals. Samples were placed on ice, centrifuged at 3000 ×*g*, and plasma aliquoted and frozen at −70 °C. A commercially available kit was used to measured plasma adiponectin levels (R&D systems, Minneapolis, Minn, USA). All samples were assayed in duplicate. The person carrying out the assays was completely blinded to the clinical information.

2.5. Statistical analysis

All statistical analyses were performed with SPSS 15.0 and MedCalc 9.6.4.0. The results were presented as counts (percentage), mean ± SD and median (interquartile range) as appropriate. Intergroup comparisons were performed using Mann–Whitney U tests, χ^2 tests or Fisher exact tests, and *t* tests as appropriate. Multivariate analysis was performed in a binary logistic-regression model with calculated odds ratio (OR) and 95% confidence interval (CI). For multivariate analysis, we included the significantly different outcome predictors as assessed in univariate analysis. Receiver operating characteristic (ROC) curves were used to describe the predictive values with the calculated area under curve (AUC) and 95% CI. In a combined logistic-regression model, the additive benefits were estimated. A 2-tailed *P*-<0.05 was considered statistically significant.

3. Results

3.1. Study population characteristics

Eighty-six patients with severe TBI and 86 age- and gender- matched healthy individual were recruited in this study. Patients included 56 males and 30 females, aged 18–76 y with a mean age of 43.3 ± 13.9 y. The mean admission time was 3.0 ± 1.2 h (0.5–6 h). On admission, the median GCS score was 6 (2) (3–8); 42 (48.8%) patients had unreactive pupils; 48 (55.8%) patients, CT classification 5 or 6; 40 (46.5%) patients, midline shift >5 mm; 45 (52.3%) patients, abnormal cisterns; 51 (59.3%) patients, traumatic SAH; 67 (77.9%) patients, mechanical ventilation. The mean systolic arterial pressure and diastolic arterial pressure were 125.0 ± 22.3 mm Hg (72–180 mm Hg) and 77.9 ± 14.8 mm Hg (45–107 mm Hg) respectively. After admission, 15 (17.4%) patients had neurological deterioration; 38 (44.2%) patients received intracranial surgery in first 24 h. 9 (10.5%) patients were complicated with seizure. Venous blood was obtained at the mean time of 4.1 ± 1.5 h (1.0–9.4 h) after admission. The mean blood glucose level and plasma C-reactive protein level were 13.1 ± 3.1 mmol/l (5.1–21.8 mmol/l) and 15.1 ± 4.4 mg/l (6.7–26.8 mg/l) respectively. In-hospital mortality was 18.6% (16/86), 6-month mortality was 27.9% (24/86), and 44 (51.2%) patients had an unfavorable outcome at 6 months after trauma. Plasma adiponectin levels were markedly higher in all patients (20.5 ± 5.9 μg/ml; range, 10.5–41.8 μg/ml) than in healthy controls (7.7 ± 2.0 μg/ml; range, 4.4–11.9 μg/ml; $P<0.001$).

3.2. In-hospital mortality prediction

Table 1 showed that the patients with higher in-hospital mortality had lower GCS score, higher blood glucose level, plasma C-reactive protein level and plasma adiponectin level, and also had higher percentage of unreactive pupils on admission, CT classification 5 or 6, abnormal cisterns on initial CT scan, midline shift >5 mm on initial CT scan, traumatic SAH on initial CT scan and mechanical ventilation. A multivariate analyses selected GCS score (OR, 0.325; 95% CI, 0.159–0.663; $P<0.001$) and plasma adiponectin level (OR, 1.318; 95% CI, 1.049–1.629; $P=0.008$) as the independent predictors for in-hospital mortality of patients.

Fig. 1 showed that plasma adiponectin level had high predictive value for in-hospital mortality of patients. Its predictive value was similar to GCS score's (AUC, 0.902; 95% CI, 0.819–0.956; $P=0.435$). In a combined logistic-regression model, adiponectin improved AUC of GCS score to 0.951 (95% CI, 0.882–0.986), but the differences were not significant ($P=0.161$).

3.3. 6-Month mortality prediction

Table 2 showed that the patients with higher 6-month mortality had lower GCS score, higher blood glucose level, plasma C-reactive protein level and plasma adiponectin level, and also had higher percentage of unreactive pupils on admission, CT classification 5 or 6, abnormal cisterns on initial CT scan, midline shift >5 mm on initial CT scan, traumatic SAH on initial CT scan and mechanical ventilation. A multivariate analyses selected GCS score (OR, 0.303; 95% CI, 0.151–0.579; $P<0.001$) and

Table 1
Factors associated with in-hospital mortality.

	Non-survivors	Survivors	*P* value
Cases	16	70	
Sex (male/female)	11/5	45/25	NS
Age (y)	44.1 ± 19.6	43.1 ± 12.4	NS
GCS score on admission	4 (2)	7 (2)	<0.001
Pupils unreactive on admission	14 (87.5%)	28 (40.0%)	0.001
CT classification 5 or 6	13 (81.3%)	35 (50.0%)	0.023
Abnormal cisterns on initial CT scan	14 (87.5%)	31 (44.3%)	0.002
Midline shift >5 mm on initial CT scan	13 (81.3%)	27 (38.6%)	0.002
Traumatic SAH on initial CT scan	14 (87.5%)	37 (52.9%)	0.011
Neurological deterioration	5 (31.3%)	10 (14.3%)	NS
Mechanical ventilation	16 (100.0%)	51 (72.9%)	0.018
Intracranial surgery in 1st 24 h	9 (56.3%)	29 (41.4%)	NS
Seizure	3 (18.8%)	6 (8.6%)	NS
Admission time (h)	2.7 ± 1.1	3.1 ± 1.2	NS
Plasma-sampling time (h)	3.8 ± 1.2	4.1 ± 1.5	NS
Systolic arterial pressure (mm Hg)	133.4 ± 23.0	123.0 ± 21.9	NS
Diastolic arterial pressure (mm Hg)	82.8 ± 15.6	76.7 ± 14.5	NS
Blood glucose level (mmol/l)	15.0 ± 3.3	12.7 ± 2.9	0.006
Plasma C-reactive protein level (mg/l)	17.8 ± 4.2	14.5 ± 4.3	0.006
Plasma adiponectin level (μg/ml)	27.2 ± 7.5	19.0 ± 4.3	<0.001

Numerical variables were presented as median (interquartile range) or mean ± SD. Categorical variables were expressed as counts (percentage). Numerical variables were analyzed by Mann–Whitney U-test or unpaired Student *t* test. Categorical variables were analyzed by χ^2 test or Fisher exact test. GCS indicates Glasgow Coma Scale; CT, computerized tomography; SAH, subarachnoid hemorrhage.