The correlation of insulin resistance with the cerebral injury and stress reaction in patients with traumatic brain injury

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ABSTRACT

Objective: To study the correlation of insulin resistance with the cerebral injury and stress reaction in patients with traumatic brain injury (TBI). **Methods**: 78 patients who were diagnosed with acute traumatic brain injury in our hospital between May 2014 and August 2016 were selected as the TBI group, and 90 healthy volunteers who received physical examination during the same period were selected as the control group. The peripheral blood was collected to detect glucose, insulin and nerve injury marker molecules, stress hormones as well as oxidative stress reaction products, and the insulin resistance index (HOMA-IR) was calculated. **Results:** The HOMA-IR index of TBI group was significantly higher than that of control group ($P<0.05$); serum neuron-specific enolase (NSE), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), S100β, myelin basic protein (MBP), glucagon, growth hormone, cortisol, malondialdehyde (MDA) and 8-hydroxy-deoxyguanosine (8-OHdG)levels of TBI group were significantly higher than those of control group ($P<0.05$); serum NSE, UCH-L1, S100β, MBP, glucagon, growth hormone, cortisol, MDA and 8-OHdG levels of patients with high HOMA-IR were significantly higher than those of patients with low HOMA-IR ($P<0.05$). **Conclusion:** The insulin resistance increases significantly in patients with traumatic brain injury, and is closely related to the degree of cerebral injury and stress reaction.

1. Introduction

Traumatic brain injury is a traumatic disease with high morbidity and mortality rates[1,2], but the key pathological link that influences the disease outcomes is not fully clear. Posttraumatic hyperglycemia is considered as the important factor that affects the prognosis of traumatic disease, there will be posttraumatic hyperglycemia during the illness development and change in patients with traumatic brain injury, and to control the blood glucose level by intensive insulin treatment has been increasingly used in the treatment of traumatic brain injury[3]. The occurrence of traumatic hyperglycemia is not caused by insufficient insulin secretion, and on the contrary, the insulin secretion significantly increases in the process of traumatic brain injury, and there is significant insulin resistance in the body[4]. When the traumatic brain injury occurs, the locus coeruleus-sympathetic nerve-adrenal medulla axis and the hypothalamic-pituitary-adrenal cortex axis are activated and cause the secretion of a large amount of glucocorticoid, growth hormone, glucagon and other blood glucose-increasing hormones, which results in the decreased insulin sensitivity and elevated blood glucose levels. In the following study, in order to define the correlation between insulin resistance and disease in patients with traumatic brain injury, the correlation of insulin resistance with the cerebral injury and stress reaction in patients with traumatic brain injury was analyzed.

2. Materials and methods

2.1. Research subjects

78 patients who were diagnosed with acute traumatic brain injury in our hospital between May 2014 and August 2016 were selected as the TBI group of the study, all of whom were with clear traumatic brain injury history, admitted to the hospital within 8 h after injury, and proven to be with traumatic brain injury after the imageological examination; the following patients were ruled out: those associated

with thoracic or abdominal injury, those associated with heart, liver and kidney dysfunction and those associated with the history of diabetes mellitus or COPD and other chronic diseases. 90 healthy volunteers who received physical examination in our hospital during the same period were selected as the control group. TBI group included 49 male cases and 29 female cases that were 25–56 years old; control group included 58 male cases and 32 female cases that were 28–55 years old. General data were not significantly different between the two groups of subjects (P>0.05).

2.2. Research methods

2.2.1. Blood sample collecting methods

5 mL peripheral venous blood was collected from TBI group immediately after admission and divided into two, one was let stand at room temperature for 30 min and then centrifuged to separate serum and store it in a -70℃ refrigerator, and the other was added in heparin for anticoagulation and then used for glucose and insulin level detection immediately.

2.2.2. Insulin resistance evaluation methods

Glucose oxidase method was used to determine blood glucose content, insulin and C-peptide levels were detected by radioimmunoprecipitation kits, and hemostasis model IR index (HOMA-IR) was used to assess the degree of insulin resistance: HOMA-IR = insulin level　glucose level / 22.5.

2.2.3. Serum traumatic brain injury index and stress index detection methods

Enzyme-linked immunosorbent assay kits were used to detect neuron-specific enolase (NSE), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), S100β, myelin basic protein (MBP), malondialdehyde (MDA) and 8-hydroxy-deoxyguanosine (8-OHdG) levels in serum samples.

2.3. Statistical analysis

SPSS21.0 software was used to input HOMA-IR and serum

indexes, the median of HOMA-IR of patients with TBI was calculated, patients with HOMA-IR > median were judged as those with high HOMA-IR, and patients with HOMA-IR < median were judged as those with low HOMA-IR.

3. Results

3.1. Insulin resistance of two groups of subjects

HOMA-IR of TBI patients was (7.59±0.93) and HOMA-IR of control group of healthy volunteers was (2.28±0.42). Comparison of HOMA-IR index between two groups of subjects was as follows: the HOMA-IR of TBI group was significantly higher than that of control group. Differences in HOMA-IR were statistically significant between TBI group and control group, t=25.952, P<0.05.

3.2. Serum nerve injury marker molecule levels of two groups of subjects

Analysis of serum nerve injury marker molecules NSE, UCH-L1, S100β and MBP between two groups of subjects was as follows: serum NSE, UCH-L1, S100β and MBP levels of TBI group were significantly higher than those of control group. Differences in serum NSE, UCH-L1, S100β and MBP levels were statistically significant between two groups of subjects (P<0.05) (Table 1).

Analysis of serum NSE, UCH-L1, S100β and MBP between TBI group of patients with different insulin resistance was as follows: serum NSE, UCH-L1, S100β and MBP levels of patients with high HOMA-IR were significantly higher than those of patients with low HOMA-IR. Differences in serum NSE, UCH-L1, S100β and MBP levels were statistically significant between TBI group of patients with different insulin resistance (P<0.05) (Table 2).

3.3. Serum stress hormone as oxidative stress product levels of two groups of subjects

Analysis of serum stress hormones glucagon, growth hormone

Table 1

Comparison of serum nerve injury marker molecules between two groups of subjects (ng/mL,$\bar{x}\pm s$).

Groups	n	NSE	UCH-L1	S100β	MBP
TBI group	78	64.95±9.61	6.58±0.93	2.42±0.39	8.51±0.93
Control group	90	13.22±1.85	1.04±0.15	0.77±0.09	2.14±0.32
t		35.965	41.822	22.385	29.581
P		<0.05	<0.05	<0.05	<0.05

Table 2

Comparison of serum nerve injury marker molecules between TBI group of patients with different insulin resistance (ng/mL,$\bar{x}\pm s$).

HOMA-IR levels	n	NSE	UCH-L1	S100β	MBP
High HOMA-IR	39	79.52±10.52	8.93±1.14	3.19±0.48	10.25±1.42
Low HOMA-IR	39	48.29±6.79	4.28±0.62	1.72±0.24	6.28±0.93
t		8.398	11.284	8.741	7.692
P		<0.05	<0.05	<0.05	<0.05

and cortisol as well as oxidative stress products MDA and 8-OHdG between two groups of subjects was as follows: serum glucagon, growth hormone, cortisol, MDA and 8-OHdG levels of TBI group were significantly higher than those of control group. Differences in serum glucagon, growth hormone, cortisol, MDA and 8-OHdG levels were statistically significant between two groups of subjects ($P<0.05$) (Table 3).

Analysis of serum glucagon, growth hormone, cortisol, MDA and 8-OHdG between TBI group of patients with different insulin resistance was as follows: serum glucagon, growth hormone, cortisol, MDA and 8-OHdG levels of patients with high HOMA-IR were significantly higher than those of patients with low HOMA-IR. Differences in serum glucagon, growth hormone, cortisol, MDA and 8-OHdG levels were statistically significant between TBI group of patients with different insulin resistance ($P<0.05$) (Table 4).

4. Discussion

Traumatic brain injury outcome is under the influence of many factors, the posttraumatic elevated blood sugar level is one of the important factors influencing the prognosis of traumatic brain injury, and continuously elevated blood sugar levels can increase the mortality and morbidity[5–7]. There is the widespread blood sugar elevation in traumatic diseases, and the occurrence of high blood sugar is mainly associated with the aggravated insulin resistance after traumatic stress. The characteristics of insulin resistance are that the sensitivity and reactivity of systemic tissues and organs to insulin reduce, insulin-stimulated glucose uptake and utilization are with obstacles, and the compensatory insulin secretion increases. The locus coeruleus-sympathetic nerve-adrenal medulla axis and the hypothalamic-pituitary-adrenal cortex axis are the target endocrine gland axis significantly activated in the process of traumatic brain injury, the former can significantly increase the glucagon and growth hormone secretion and increase blood sugar levels, and the latter can increase the cortisol secretion and blood glucose levels. Existing domestic research reports show that blood sugar levels can

accurately assess the severity of severe traumatic brain injury[8,9]. But the effect of insulin resistance on the development of traumatic brain injury is unclear. In the study, analysis of the insulin resistance in patients with traumatic brain injury confirmed that the HOMA-IR index of TBI group was significantly higher than that of control group. This means that there is obvious insulin resistance in patients with traumatic brain injury, and the occurrence of insulin resistance may be related to the activation of target endocrine gland axis caused by the stress reaction after traumatic brain injury.

Nerve injury in the process of traumatic brain injury is closely related to the hyperglycemia level, insulin resistance is the critical pathological link leading to the elevated blood sugar levels in patients with traumatic brain injury, but the relationship between insulin resistance and traumatic brain injury is not clear. Traumatic brain injury can cause neuron and glial cell destruction as well as blood brain barrier damage, and the NSE, UCH-L1, S100β, MBP and other molecules in the cells enter into the outside and then enter into the blood circulation through the damaged blood brain barrier. Both NSE and UCH-L1 are the metabolic enzymes positioning in the neurons, the former is involved in the adjustment of the glycolytic pathway in neurons, the latter is involved in the composition of ubiquitin proteasome system in neurons, and both are of great value for the neuron growth and development as well as function maintenance[10,11]; S100β is a kind of acidic calcium-binding protein existing in neurons and glial cells at the same time, and it is involved in the regulation of intracellular calcium ion homeostasis and cell skeleton components[12,13]; MBP is a type of strongly basic membrane protein in the glial cells that can adjust the glial cell function[14]. In the study, analysis of the above serum nerve injury marker molecules in patients with TBI confirmed that serum NSE, UCH-L1, S100β and MBP levels of TBI group were significantly higher than those of control group ($P<0.05$). In order to define the correlation between insulin resistance and the severity of traumatic brain injury, the relationship between HOMA-IR and serum brain injury molecule levels was further analyzed in the study, and the results showed that serum NSE, UCH-L1, S100β and MBP levels of patients with high HOMA-IR were significantly higher than those

Table 3

Comparison of serum stress hormones as oxidative stress products between two groups of subjects ($\overline{x}\pm s$).

Groups	n	Glucagon (pg/mL)	Growth hormone (μg/mL)	Cortisol (nmol/L)	MDA (μmol/L)	8-OHdG (ng/mL)
TBI group	78	189.54±22.35	5.58±0.75	545.61±78.74	7.94±0.93	52.94±7.62
Control group	90	94.41±10.25	1.95±0.25	193.42±22.58	2.52±0.36	16.95±2.652
t		9.812	26.855	33.582	19.284	21.396
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 4

Comparison of serum stress hormones as oxidative stress products between TBI group of patients with different insulin resistance ($\overline{x}\pm s$).

HOMA-IR levels	n	Glucagon	Growth hormone	Cortisol	MDA	8-OHdG
High HOMA-IR	39	232.67±29.57	7.12±0.94	724.21±93.62	9.29±1.14	65.92±9.32
Low HOMA-IR	39	134.21±15.86	3.92±0.48	367.41±52.69	6.32±0.93	39.32±4.86
t		8.285	8.938	9.582	7.281	9.182
P		<0.05	<0.05	<0.05	<0.05	<0.05

of patients with low HOMA-IR ($P<0.05$). This means that the degree of insulin resistance is associated with the severity of traumatic brain injury, and the heavier the degree of insulin resistance, the more nerve injury marker molecules released into the blood circulation and the severer the nerve injury degree.

The occurrence of insulin resistance in patients with traumatic brain injury is associated with the activation of post-traumatic stress reaction. The external trauma is a strong stressor for the body, which can activate the locus coeruleus-sympathetic nerve-adrenal medulla axis and the hypothalamus-pituitary-adrenal cortex axis, then mediate stress reaction and cause insulin resistance through secreting a variety of hormones. The endocrine hormones that are released by activated locus coeruleus-sympathetic adrenal medulla axis are the glucagon and growth hormone, and the endocrine hormone released by hypothalamus-pituitary-adrenal cortex axis is cortisol[15]. During the activation of stress reaction, the secretion of above hormones is abnormal, and there will also be severe oxidative stress and massive production of reactive oxygen species. Excessively accumulated reactive oxygen species in local tissue can cause the peroxidation damage of lipid and nucleic acid compositions in cells, and produce the corresponding oxidative stress products MDA and 8-OHdG at the same time[16,17]. In the study, analysis of above stress hormones and oxidative stress products in serum of patients with TBI confirmed that the serum glucagon, growth hormone, cortisol, MDA and 8-OHdG levels of TBI group were significantly higher than those of control group ($P<0.05$). In order to define the correlation between insulin resistance and stress reaction, the relationship of HOMA-IR with serum stress hormone and oxidative stress product levels was further analyzed in the study, and the results showed that serum glucagon, growth hormone, cortisol, MDA and 8-OHdG levels of patients with high HOMA-IR were significantly higher than those of patients with low HOMA-IR ($P<0.05$). This means that the degree of insulin resistance is closely related to the degree of stress reaction in patients with traumatic brain injury, and the severer the degree of insulin resistance, the severer the degree of stress reaction.

Based on above discussion, it is believed that there is significant insulin resistance in patients with traumatic brain injury, and the aggravation of insulin resistance is closely related to the aggravation of cerebral injury and stress reaction. The secretion of stress hormones and the generation of oxidative stress products are involved in the insulin resistance, and the elevated blood glucose caused by insulin resistance is involved in the nerve injury.

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