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Can Adropin Peptides Be A Biomarker For Traumatic Brain Injury? A Prospective Study

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ABSTRACT

Traumatic brain injury continues to be a severe health problem worldwide due to its significant mortality and morbidity. Computed Tomography and Glasgow coma scale are the main diagnostic methods used to determine the severity of traumatic brain injury today. However, both methods have their limitations. Therefore, biomarkers that can reliably reflect the extent of post-traumatic brain injury and microscopic pathological events have been sought for a long time.Our study aims to investigate whether serum adropin levels can be a biomarker used in adult head trauma.

The study was designed as a prospective study of adult patients admitted to the emergency department with isolated head trauma. A demographic information form was filled for each individual participating in the study. All patient evaluations were made by emergency medicine specialists. The study population consisted of patients who required computerized brain tomography at the time of admission. The blood samples were obtained within the first hour of admission to the emergency room.

Adropin levels in the patient group were statistically significantly higher than in the control group (p=<0.001). Besides, no statistically significant difference was found in serum Adropin levels between the patient group who had bleeding and fractures determined in the brain tomography and those with no pathological findings (p=0.723).

We think that adropin may have protective or curative effects on the human brain.

Keywords: Adropin, brain trauma, computed tomography

Introduction

Traumatic brain injury (TBI) is a change in brain function due to an external force. TBI continues to be a severe health problem worldwide due to its significant mortality and morbidity (1,2). Accurate determination of the initial severity of brain injury after head trauma is crucial to balancing the risks and benefits of treatment (3).

Computer Tomography (CT) and Glasgow Coma Scale (GCS) are the main diagnostic methods used to determine the severity of TBI today (4,5). However, both methods have their limitations [(6)]. For example, CT can capture dynamically developing snapshots of TBI but cannot detect pathological lesions occurring at the microscopic level (7).Therefore, biomarkers that can reliably reflect the extent of post-traumatic brain injury and microscopic pathological events have been sought for a long time. Thanks to these biomarkers, it will be easier for patients to decide whether to have computerized brain tomography or not.

Many biomarkers with the potential to be used in the diagnosis of TBI have been investigated. However, there is no study on serum adropin levels. Adropin is a newly identified metabolic hormone involved in the regulation of lipid metabolism, encoded by the energy homeostasis-associated gene (ENHO). It was first isolated from liver and brain tissues by Kumar et al. in 2008 (8).Various human and animal experiments have been conducted to investigate the effects of adropin on energy homeostasis or peripheral tissues (9,10,11,12). However, the effects of adropin on the central nervous system remain unclear.

Some animal experiments have been performed to evaluate the effects of adropin on the central nervous system. In one of these studies, adropin was demonstrated to protect the blood-brain barrier via Notch1/Hes1 pathway after intracerebral hemorrhage in rats[(13)]. In another study, adropin was found to have a protective effect against dysfunction in the blood-brain

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barrier (BBB) in rats exposed to ischemia-like conditions (14).

When the literature is examined, there is no study on the effects of adropin on the human brain. Our study aimed to investigate whether serum adropin levels are a biomarker that can be used in adult head trauma.

Materials and Methods

Study Design and Settings: The study is prospective research including adult patients admitted to Regional Training and Research Hospital Emergency Department with isolated head trauma between April 2020 and June 2021. The local ethics committee approved the study (The protocol number that was attributed by the ethics committee is 2019/13-125 and the date of approval by the ethics committee is 21.10.2019), which was performed following the VMA Declaration of Helsinki, 1964, and later revisions. Informed consent was obtained from all participants or their relatives who participated in the study. Fifty-four people with isolated head trauma who presented to the emergency department within 6 hours of injury were included in the study. Thirty-six healthy volunteers, matched with the experimental group according to gender and age as the control group, were included. The patient evaluations were made by emergency medicine specialists. All patients were carefully evaluated for eligibility for the study. The study population consisted of patients who were required to undergo brain computed tomography (BCT) at the time of admission. The decision to perform CBT was made according to the Nexus II criteria. BCT scans were interpreted by a neuroradiologist. Patients with isolated head trauma and older than 18 years were included in the study. Exclusion criteria from the study were a history of head trauma longer than 24 hours, multiple traumas, head trauma with cerebrovascular disease, a history of seizures, and penetrating head trauma. Patients younger than 18 years of age and pregnant women were also not included. Blood samples were taken from all patients and control groups participating in the study into tubes that did not contain anticoagulant. The patients were grouped according to the computerized brain tomography results. Afterwards, those with bleeding and fractures on tomography were compared in terms of Adropin levels compared to those who had no findings in their tomography.

Analysis of Adropin: The blood samples were obtained within the first hour of admission to the emergency room. After the samples were taken into tubes without anticoagulant, they were kept at room temperature for approximately 30 minutes and then centrifuged at 1000xg for 20 minutes at +4^{o}C through the ELISA kit instructions we used. The remaining serum portions were transferred to Eppendorf tubes and raised to -80^{o}C until the date of the study. Adropin was studied by Human Adropin ELISA Kit (USCN, China, Cat.No: SEN251Hu) brand kit as per the manufacturer's procedures. Laboratory personnel performing ELISA tests were blind to clinical data.

Demographic Information Form: The Demographic Information Form contains various information about the individuals who participated in the study. The forms were recorded by the emergency specialist who evaluated the patient. In these forms, parameters such as participants' gender, age, trauma mechanism, CT results, adropin levels, nexus criteria, and time from admission to the emergency room to sample collection were included.

Statistical Analysis: IBM SPSS statistical program (v.20.0; SPSS Inc., Chicago, IL, USA) was used to analyze the data obtained in the study. Parametric variables were expressed as mean and standard deviation values, while categorical variables were presented as frequencies and percentages. The normality distribution of the data was analyzed with the Kolmogorov-Smirnov test. Independent sample t-test was used to compare two-group and normally distributed independent data, and the Mann-Whitney U test was preferred for data that were not normally distributed. A p-value less than 0.05 was considered statistically significant in all interpretative analyses.

Results

Fifty-four patients (17 women, 37 men) with isolated head trauma and 34 healthy controls (19 women, 16 men) were included in the study. There was no statistically significant difference between head trauma patients and trauma controls regarding age, gender, or race. In terms of the mechanism of injury, falling ranked the first in patients (50%). In the patient group, blood collection time for adropin was, on average, 30 minutes after trauma. The decision to perform CBT was made according to the Nexus II criteria. Scalp hematoma was the first reason, with 66.7%, among the causes of BCT. Adropin levels in the

Table 1. Basic Demographic and Clinical Characteristics of The Patient and Control Groups

Variables	Patient (n=54)	Control (n=34)	P value
Sex (K) n (%)	17 (%31,5)	19 (%56)	
Age (Yıl) X ± SS	46,50 ± 2,77	38,26 ± 2,40	0.106a
Adropin (pg/ml) X ± SS	3775,45 ± 98,23	3100,73± 123,55	<0.001b
Blood collection time (minute), median (min-max)	30 (15-240)		
Injury Mechanism			
Fall n (%)	27 (%50)		
In-vehicle traffic accident n (%)	12 (%22,2)		
Non-vehicle traffic accident n (%)	4 (%7,4)		
Sports injury n (%)	2 (%3,7)		
to beat n (%)	6 (%11,1)		
Unknown n (%)	3 (%5,6)		
Nexus Criteria			
Age>65 n (%)	16 (%29,6)		
Altered Level of Alertness.n (%)	12 (%22,2)		
Evidence of significant Skull Fracturen (%)	4 (%7,4)		
Abnormal behavior.n (%)	3 (%5,6)		
Scalphematoman (%)	36 (%66,7)		
Coagulopathy. n (%)	3 (%5,6)		
Neurologic deficitn (%)	1 (%1,9)		
Recurrent or forceful vomiting.n (%)	4 (%7,9)		

p[a] Man-Whitney U Test, p[b]independent sample t-test

Table 2. CT Findings In The Patient Group

	N	%
No CT findings	37	68,5
Bleeding	10	18,5
Skull Fracture	7	13

patient group were statistically significantly higher than in the control group (p=<0.000). The demographic and laboratory data of the study participants are summarized in Table 1 (Table 1).

The BCT findings in the patient group were as follows; no pathological CT findings in 68.5% (n=37), bleeding in 18.5% (n=10), and bone fracture in 13% (n=7) (Table 2).

An independent sample t-test was used to determine the level of significance of the change in Adropin levels in the patient group who had bleeding and fracture determined in the brain tomography compared to those with no pathological findings. As a result of the analysis, no statistically significant difference was observed between the groups (p=0.723) (Table 3).

Discussion

One of the most critical difficulties experienced by the emergency physician in managing patients admitted to the emergency department with head trauma is determining whether the patient has an indication for imaging with BCT. Computed tomography has become the first-line examination for the early diagnosis of trauma patients. It can identify various injuries rapidly and with high sensitivity. However, BCT has limitations such as radiation and cost. In addition, BCT cannot detect pathological lesions occurring at the microscopic level (7,15). Therefore, biomarkers that can reliably reflect the extent of post-traumatic brain injury and microscopic pathological events have been examined. We think that the recently found adropin peptide may be a biomarker indicating traumatic brain injury. In this context, the main

Table 3. Adropin Levels According to CT Results In The Patient Group

	N	Adropin Mean	SS	p
CT finding is not present	37	3799,5162	121,28549	0,723
CT finding ispresent	17	3723,1009	171,01291	

findings of our study are as follows: (1) Adropin levels in the patient group were statistically significantly higher than the control group (p=<0.000) (2). There was no statistically significant difference in serum Adropin levels of those with bleeding and fractures determined on the brain tomography and those with no pathological findings (p=0.723) in the patient group.

For the first time, Kumar et al. revealed that adropin was synthesized from liver and brain tissues[8]. Adropin has a molecular weight of 4499.9 Da and is composed of 76 amino acids. The amino acid sequence is exactly the same in humans, rats and mice. It was noticed and isolated during high-fat feeding studies on type C57BL/6J mice. As a result of the studies, a significant increase in the amount of blood serum adropin and visible changes in insulin response and glucose intolerance were noted in mice on a high-fat diet. Based on the close relationship between vascular function and insulin sensitivity in further studies, whether adropin has a direct effect on endothelial tissue has been the subject of research (10,16).

Later, Aydın et al. examined how diabetes affected adropin expression in rats' brains, cerebellum, kidneys, heart, liver, and pancreas tissues. The study indicated increased adropin immunoreaction in the cerebellum,heart,brain, kidneys, pancreas and liver in diabetic rats compared to control subjects. Also, adropin levels were found to be higher in the brain (vascular area,neuroglial cells, pia matter and neurons) and cerebellum (neuroglial cells, Purkinje cells, vascular areas, and granular layer) of diabetic rats compared to control rats (16).

Furthermore, Yu et al. investigated the role of adropin in collagenase-induced intracerebral hemorrhage in mice. Adropin has been shown to reduce water content in the brain and improve neurological functions. Adropin preserved the functionality of the blood-brain barrier by decreasing the extravasation of albumin and increasing the expression of N-cadherin. The study also revealed that in vivo degradation of Hes1 and Notch1 abolished the protective effects of adropin. In conclusion, it was shown in the study that adropin protects the blood-brain barrier and may have a potential therapeutic value for intracerebral hemorrhage (13).

There are other studies examining the effects of adropin on the rat brain (14,17). However, there are no studies performed to investigate the effects of adropin on the human brain. Our study found that serum adropin was higher in isolated head trauma patients than in healthy volunteers, and this elevation was statistically significant. Besides, there was no statistically significant difference in serum Adropin levels in the patient group with bleeding and fractures determined on the brain tomography and those with no pathological findings. We think that the reason for this may be the limited number of equivalents in our study. Although our study is limited in terms of the number of participants, we think that it is crucial because it is the first study in this field. We also think that this study will lead to more comprehensive studies investigating the effects of adropin on the human brain.

The management of head trauma is challenging. Especially, it is a severe issue for clinicians to decide in which cases to have BCT. In this context, biomarkers have gained importance in identifying the patients who predict the severity of head trauma and need BCT. Various biomarkers have been investigated in this regard. However, a biomarker that can be used to identify patients who need CBT is not yet available. Could adropin be one of the biomarkers that should be investigated in this regard? In our opinion, it might be. Just like in rats, we think that adropin may have protective or curative effects on the human brain. After all, post-traumatic adropin levels were higher in patients in our study compared to healthy volunteers. Of course, it is necessary to obtain more precise and reliable data by performing extensive studies on the subject.

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