Use of Biomarkers in Early Detection and Treatment of Concussion

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Abstract

Background
Athletics are an integral part of the fabric of both our country and the world. The risk of sustaining a concussion, defined as a traumatically induced, transient disturbance of brain function secondary to minor or major trauma to the head, is an inherent risk factor in athletics. The use of biomarkers in concussion diagnosis is an emerging field and may lead to earlier diagnosis of concussion and improve rehabilitation and return to play treatments.

Methods
A narrative literature review was used to investigate the use of biomarkers in detection and treatment of concussions. Specifically, whether the use of biomarkers allows for earlier detection and treatment of concussions and guide return to play recommendations.

Results
Higher levels of tau protein within 6 hours of head injury was a predictor of longer return to play times after sustaining a sport related concussion. S100B has been shown to be useful in distinguishing sport-related concussion from sport-related exertion. Additional biomarkers that have been studied have shown no benefit in diagnosis and treatment of concussion.

Conclusion
The diagnosis of concussion remains largely one of clinical presentation. In the future, ancillary testing may have the potential to aid in diagnosis, particularly once the technology and testing potential becomes widely available.

Background

Athletics are an integral part of the fabric of both our country and the world. With any sport inherent dangers are present. One of those dangers is the risk of sustaining a concussion secondary to minor or major trauma to the head. Concussions are a traumatically induced, transient disturbance in brain function. While research has continued to advance, there continues to be no consensus on how to diagnose and treat individuals with concussions. Athletes are potentially placed at increased risk of recurrent brain injury should they be misdiagnosed and allowed to return to play too early.

The use of biomarkers continues to be a fluid and evolving area of concussion research. The goal of biomarker use is to allow for earlier concussion detection and improve return to play procedures. Previous studies have focused on various aspects of the use of biomarkers in the diagnosis and treatment of concussion. In one study it was found that higher levels of tau protein within 6 hours of head injury was a predictor of longer return to play times after sustaining a sport related concussion. (Gill et. al. 2017). Another biomarker used in the study of concussion includes S100B which has been shown to be useful in distinguishing sport-related concussion from sport-related exertion (Kiechle et. al., 2014). In other studies, the use of Beta-amyloid peptide 42, total tau, S100 Calcium Binding Protein (S100B), Ubitquitin C-terminal Hydrolase L1 (UCH-L1), Glial Fibrillary Acidic Protein (GFAP) and 2'3'-cyclic-nucleotide 3'-phosphodiesterase (CNPase) serum concentrations when accounting for different demographic factors have shown poor reliability (Asken et. al. 2018).

One disadvantage of current literature is the poor crossover between studies in their ability to compare and broadly apply results. Previous studies have looked at varying biomarkers and outcomes. Others looked at diagnosis of concussion or time to return to play amongst other variables. This limited generalizability leaves clinicians with a lack of true guidance in this diagnosis and formulation of return to play treatment and guidelines.

While concussions are not limited to athletes, the ability to properly detect and treat concussions is of paramount importance in athletics. Athletes are more likely to experience repetitive head trauma when they return to activity due to baseline change of head injury. The ability for early detection and proper treatment of concussion with the potential use of biomarkers to aid in diagnosis and treatment of closed head injuries are an important topic within athletic departments worldwide.

Methods

Objectives

The goal of this literature review is to investigate the use of biomarkers in detection and treatment of concussions. Specifically, whether the use of biomarkers allows for earlier detection and treatment of concussions and guide return to play recommendations. Six articles were reviewed to assess the utility of biomarkers in the diagnosis, treatment and return to activity of individuals suspected or confirmed to have a concussion.

Participants

All studies included in the literature review had a study population that was presented to an emergency department or athletic training facility following a head injury. Participants presented with symptoms concerning concussion following head trauma. These individuals subsequently underwent blood testing looking at various biomarkers that could aid in the detection of concussion.

Data analysis

Articles for review were collected using the Oklahoma State University Center for Health Sciences Medical Library website for access to primary literature databases. The PubMed website was searched using the following terms to locate potential articles for review: *concussion, concussion biomarkers, closed head injury, closed head injury biomarkers.* A secondary search was performed using the initial articles obtained. All articles reviewed were from peer reviewed journals. Articles from non-peer reviewed journals were excluded. Due to the relatively small sample size of research in this area of study, no further exclusion criteria were used in the initial article search.

Interpretation

Articles were individually reviewed and evaluated by the primary author. Initially, articles were reviewed to evaluate sample size and demographics. The listed primary, secondary and observed outcomes were then identified, followed by a review of the methodology, data, and conclusions.

Literature Review

Historical use of Biomarkers

It is estimated that there are more than 3.5 million emergency department visits for traumatic brain injury per year (Rubenstein et. al, 2017). Historically, the diagnosis of concussion has largely been based on symptomatology and clinical suspicion. This has made diagnosis difficult with the subjective and nonspecific nature of self-reported symptoms (Meier et. al. 2017). Additionally, treatment has largely been based on resolution of symptoms and ability to tolerate physical exertion without reproduction of symptoms. More recent research has been focused on utilization of additional tools including detection of various serum biomarkers to aid in earlier diagnosis of concussions and earlier implementation of treatment and rehabilitation.

Current Biomarkers

Current concussion research has examined a multitude of biomarkers in an attempt to aid in earlier diagnosis and treatment of concussion. These biomarkers include beta-amyloid peptide 42, Total tau, S100B, UCH-L1, GFAP, MAP2 and CNPase (Asken et. al. 2018). These studies have largely focused on athletes. An important factor in these studies is to establish a baseline,

therefore allowing researchers to study the change in these biomarkers from baseline (Meier et. al. 2017).

S100B

One of the biomarkers that has been extensively studied is the astroglial protein S100B. This protein has been used in individuals with a presumed concussion to aid in the identification of intracranial hemorrhage (Karin et. al. 2014). The difficulty in the use of this protein to aid in diagnosis is that it has been found to rise from baseline both in individuals who have sustained a concussion but also rise following exertion without concussion (Karin et. al. 2014). A study conducted in 2018 found that males express higher baseline levels of S100B than females and African Americans express higher baseline levels of S100B than other races (Asken et. al 2018). Accounting for demographic factors such as sex and race are essential in the diagnosis of concussion.

S100B has been found to discriminate concussed from control athletes at the 6-hour mark from initial head injury (Meier et. al. 2017). Another study found that S100B is found to rise from baseline in individuals who have blood drawn within 4 hours of insult. However, blood obtained greater than 4 hours after insult did not show significantly elevated levels of S100B (Asken et. al. 2018). In a study conducted by Asken et. al., a S100B level of 52 pg/mL had a sensitivity of 77.8% and specificity of 58.8% to sports related concussion. When this data was stratified by race, the value of 52 pg/mL was 72.7% sensitive and 74.6% specific in whites; however, this level was not significant in African American subjects. A value of 72 pg/mL was found to be the critical value for African Americans, thus highlighting the need for stratification based on age, gender and race.

Karin et. al. published a study in 2014 which also studied the use of S100B in diagnosis of sport related concussion. In this study they used a baseline test and obtained S100B blood levels within three hours of sustaining a concussion. It was found that a 3-hour post-concussion S100B level >0.122 ug/L and proportional increase of >45.9% were 96.7% specific for sport related concussion. Also, no significant difference from baseline levels were found following exertion in individuals who did not sustain a concussion.

Tau Protein

Tau protein is an additional biomarker that has been mentioned in multiple studies. It is involved in regulating axonal microtubule assembly and disassembly (Rubenstein et. al. 2017). Abnormal accumulation of phospho-tau deposition has been discovered in postmortem human brains in individuals who have sustained repetitive traumatic brain injuries. It has also been found in mice following blast injuries (Rubenstein et. al. 2017). This study categorized traumatic brain injury by mild (GCS 13-15), moderated (GCS 9-12) and severe (3-8). The total Tau protein level was 62.59 fg/mL in healthy controls. This level rose to 79.21 fg/mL in those with mild TBI, 84.10 fg/mL in those with moderate TBI and 79.21 fg/mL in those with severe TBI. All of these values were found to be statistically significant. Additionally, the median phospho-tau level in healthy controls was 20.85 fg/mL, 200.16 fg/mL for mild TBI, 307.19 fg/mL for moderate TBI and 294.68 fg/mL for severe TBI, which were all statistically significant.

In the study by Gill et al. published in 2017, authors found differences between 24 and 72 hours. Athletes that sustained a sports related concussion had total tau protein levels of 6.06 vs 7.89 pg/mL at 24 hours and 5.19 vs 6.94 pg/mL at 72 hours, both of which were statistically significant. However, when healthy controls were excluded, athletes with a higher total tau protein concentration had a longer return to play time compared to those with shorter return to play time. These values were correlated at 6 hours post injury (10.98 vs. 7.02 pg/mL), 24 hours (7.19 pg/mL vs 4.08 pg/mL) and 72 hours (6.29 vs 3.94 pg/mL), all of which were statistically significant. Gill et al. also found that athletes with long return to play time had a mean increase in total tau of 2.26 pg/mL at 6 hours post sport-related concussion, whereas the short return to play group had a mean reduction of 1.19 pg/mL. Lastly, it was found that a higher total tau concentration at 72 hours post-concussion was found to be a significant predictor of return to play of greater than 10 days.

UCH-L1

In a study by Meier et. al. published in 2017, authors looked at the Ubiquitin C-Terminal hydrolase-L1 (UCH-L1) biomarker. UCH-L1 was found to have significant variability from baseline in those who sustained a concussion. Meier et al. studied the variation from baseline of the UCH-L1 protein at 6 hours post-concussion. The baseline level in the control subjects was 101.30 pg/mL vs 204.35 pg/mL 6 hours post injury in those who sustained a concussion (Meier et al. 2017).

GFAP, MAP2, CNPase

Other biomarkers including glial fibrillary acid protein (GFAP), microtubule associate protein 2 (MAP2) and 2',2'-cyclic-nucleotide 3'-pshophodiesterase (CNPase) have been studied. In a study published by Asken et al., individuals studied had a baseline GFAP level of 30.1 pg/mL and post sport related concussion level of 24.7 pg/mL. In the same study, the baseline level of the MAP2 biomarker was 115.1 pg/mL vs. 105.2 pg/mL post sport related concussion and CNPase levels were too low to quantify both at baseline and post sport related concussion. These biomarkers have not been found to provide statistically significant data to aid in the diagnosis of concussion (Asken et al 2018 and Meier et al 2017).

Conclusion

The review of the literature does present some promising data that biomarkers can be used to aid in diagnosing concussions and return to activity guidelines. Currently, this field of study is in its infancy relative to other fields of medical research. The diagnosis of concussion remains largely one of clinical presentation, however supplemental modalities do appear promising that they can further aid in diagnosis.

The difficulty with using biomarkers to aid in diagnosing concussions is multifaceted. Firstly, the tests that are being performed are not available in all facilities, therefore the reliability of these biomarkers have the potential to be under or overstated. Secondly, the ability for all patients to follow-up on an outpatient basis and monitor these biomarkers may be very difficult. As a result, establishing return to activity guidelines based on biomarker trends may not be feasible.

These articles have provided hopeful insight into the future of closed head injuries and brain health with regards to diagnosis and treatment. The hope would be to minimize effects from too early return to activity and the increased risk of secondary head injuries. However, currently the diagnosis of concussion remains based on clinical symptoms alone. In the future, ancillary testing may have the potential to aide in diagnosis, particularly once the technology and testing potential becomes widely available.

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