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Traumatic Brain Injury in Sport with Special Focus on Biomarkers of Concussion Injury

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Abstract

Traumatic brain injury (TBI) is typically categorized as being mild, moderate, or severe. Over the years much of the research focus has been geared toward moderate and severe TBI as these injuries are seen most often in the clinical setting. In contrast, mild TBI is more difficult to diagnose and there is inconsistency within the literature on how exactly mild TBI should be diagnosed. Even more difficult to diagnose than mild TBI is concussion injury. Concussions have been a recent and constant news headline for the past several years as evidence suggests that repeated concussive and sub-concussive impacts due to sports play, especially American football, can result in permanent brain damage. Therefore, it is the purpose of this short communication to shed light on recent research into the discovery of an objective and reliable biomarker to assess concussion injury.

Keywords: Traumatic brain injury; Concussion; Biomarkers

Diagnosis of Traumatic Brain Injury

Traumatic brain injury (TBI) is the leading cause of death and disability in children and young adults around the world, with most TBIs caused by road traffic accidents, falls, and violence [1]. The Glasgow Coma Scale (GCS) is typically used to assess severe (GCS 3-8), moderate (GCS 9-12), and mild (GCS 13-15) TBI along with results from a computerized tomography (CT) examination or a skull X-ray if a CT scanner is not available [1]. Although the GCS appears to be appropriate for assessing severe and moderate TBI there is concern that mild TBI may be more difficult to assess [2]. For example, there is argument as to whether a GCS of 13 should be included in the category of mild or moderate TBI [3,4]. It has also been suggested that the GCS is not sensitive enough to assess mild TBI since a GCS score of 15 may be interpreted as a normal examination when a mild TBI did indeed occur [5,6].

Mild TBIs are difficult to diagnose due to the quick resolution of symptoms and the absence of objective evidence for injury using neuroimaging techniques [6–8]. Several review papers have been published in hopes of finding consistency in the literature on how to diagnose mild TBI [2,4–6,9]. These reviews have found that diagnostic criteria for determining mild TBI typically include: a clear mechanism for suspicion of injury, post traumatic amnesia (PTA) [5,6,9–11], loss of consciousness (LOC) [6,9–11], seizure [6,9], altered consciousness [5,6,9,11], focal neurological deficit [6,9,11], vomiting [4], and diffuse headache [4]. However, these sequelae are transient and can change quickly following TBI [6]. Also, PTA and LOC may be difficult to assess as the patient may not realize that he or she is experiencing these symptoms unless told by a person who witnessed the events before and after the TBI [6]. Review articles investigating mild TBI commonly come to the conclusion that the literature on the diagnostic procedures of mild TBI is inconsistent, and a more objective, concrete determination of mild TBI is required.

Concussion Injury

Concussion injury is a specific form of mild TBI defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces [7]. A person diagnosed with a concussion generally experiences at least one of the following adverse effects: somatic (e.g. headache), cognitive (e.g. feeling in a fog, vertigo), emotional (e.g. lability), physical (e.g. LOC, amnesia, fatigue), behavioral (e.g. irritability), cognitive (e.g. feeling in a fog), or sleep disturbance (e.g. insomnia) [6,7]. Based off these symptoms, several concussion diagnostic tools have been developed.

The Sport Concussion Assessment Tool–3rd edition (SCAT3) [7] and Standard Assessment of Concussion (SAC) [12] are common tests used on the side-line of sporting events to determine if a concussion has occurred. Other tests that have been developed to help diagnose concussion injury include tests of postural deficit [13], electrophysiological recordings [14–16], neuropsychological testing [17–20] and reaction time tests [21,22]. However, none of these tools are recommended for use as a stand-alone method to diagnose concussion and are not always practical for side-line assessment. Assessments for concussion must be practical, reliable, objective, and have a quick result so important on-the-field decisions can be made that both protect the injured athlete such that further and possibly permanent brain damage is not incurred [23–30], yet do not prevent an uninjured athlete from return to play (RTP).

Since concussion is among the most complex injuries in sports medicine to diagnose [7] it may be too complex to be elucidated from a single test, yet a single objective test must be sought in order to eliminate confusion and error in concussion diagnosis. A viable candidate for objective diagnosis is a biomarker of concussion injury. Although there are many biomarker candidates, the most useful and practical biomarkers are found in systemic circulation such that the risks of obtaining cerebral spinal fluid (CSF) can be avoided and analysis of the biomarker can occur on the side-line of an athletic

event. With this in mind, the pool of currently discovered biomarkers that may be used for concussion assessment is significantly narrowed (Figure 1).
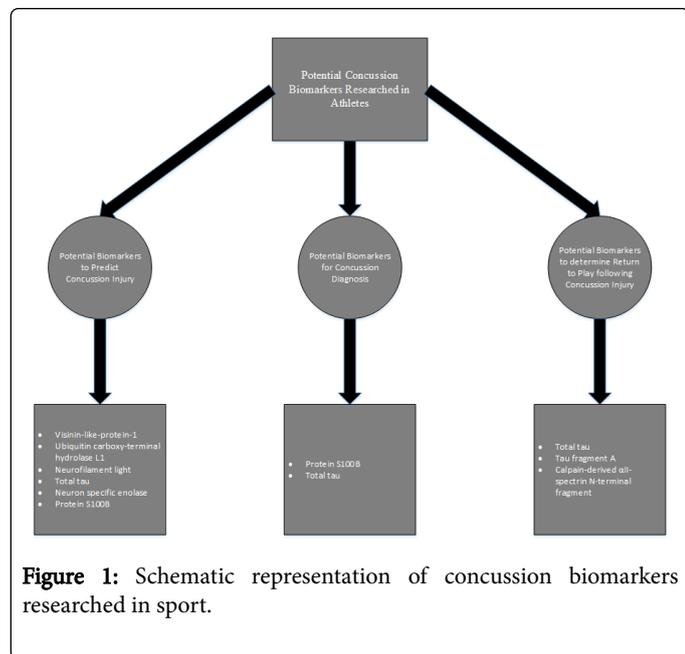

Figure 1: Schematic representation of concussion biomarkers researched in sport.

Potential Concussion Biomarkers

Concussion biomarkers that have been studied in systemic circulation of athletes include: brain-derived neurotrophic factor (BDNF) [31], heart-type fatty acid binding protein (h-FABP) [31], serum visinin-like protein-1 (VILIP-1) [32], β-2 transferrin [33], ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) [33], neurofilament light (NFL) [34,35], total tau (T-tau) [36], tau fragment A (Tau-A) [37], tau fragment C (Tau-C) [37], glial fibrillary acidic protein (GFAP) [31,38], myelin basic protein (MBP), calpain-derived αII-spectrin N-terminal fragment (SNTF) [39], neuron-specific enolase (NSE) [31,36,40–44], and protein S100B (S100B) [31,33,36,38,40–50]. Of these studies only a marked increase in VILIP-1 [32], UCH-L1 [33], NFL [34], SNTF [39], T-tau [36], Tau-C [37], NSE [31,32,36,40–44], and S100B [32,33,36,38,40–48] was found following sport. Furthermore, only VILIP-1 [32], SNTF [39], T-tau [36], Tau-A [37], Tau-C [37], NSE [36], and S100B [36,46] have been examined to determine efficacy in their ability to diagnose concussion injury.

The majority of studies investigating the efficacy of biomarkers to diagnose concussion have been conducted on professional ice hockey players [32,36,37, 39]. These studies have shown the following results: VILIP-1 did not change 1 h after concussion compared to pre-season levels and decreased between 12 and 36 h post-concussion suggesting that VILIP-1 is not likely a useful biomarker for the diagnosis of concussion [32], compared to pre-season levels T-tau and S100B increased significantly following concussion while no significant change occurred with NSE [36], Tau-C levels increased significantly following concussion, and although Tau-A levels did not increase after concussion, the levels were correlated with the duration of post-concussive symptoms [37], SNTF levels rose significantly following concussion and correlated with duration of post-concussive symptoms [39]. The only other study comparing baseline biomarker levels to those after concussion injury was conducted in football, soccer, ice hockey, and basketball players [46]. This study found that S100B increased significantly three hours after concussion injury but did not correlate well with post-concussive symptoms [46].

Predictive Biomarkers

Based off current research, the biomarkers VILIP-1, UCH-L1, NFL, T-tau, NSE, and S100B may be useful in detecting sub-concussive impacts leading to concussive injury since they have been show to increase in athletes following sport competition without the incidence of concussion [31–34,36,38,40–45,47–49]. Longitudinal studies following the changes of these biomarkers leading up to concussion will help in determining if they can predict the occurrence of concussion. These biomarkers could then be used as a tool for prevention by having an athlete take games off when their biomarker levels become too high, thereby preventing concussion injury from occurring.

Diagnostic Biomarkers

S100B and T-tau currently have the most promise as potential biomarkers for the diagnosis of concussion [36,46]. The specificity and sensitivity of these two biomarkers have been assessed within a few hours following concussion injury using the area under the receiver operating characteristic curve (AUC). Coefficients for AUC range from 0 (no sensitivity or specificity) to 1.0 (perfect sensitivity and specificity). The diagnostic ability of the biomarkers can be deemed worthless to excellent using specific AUC coefficient ranges as indicated in Table 1.

AUC Coefficient	Rank
1.0	Perfect Test
0.9–1.0	Excellent Test
0.8-0.9	Good Test
0.7–0.8	Fair Test
0.6–0.7	Poor Test
≤ 0.6	Worthless Test

Table 1: Range of area under the receiver operating characteristic curve coefficients ranked into worthiness of test categories.

Twenty-eight male professional ice hockey players from the Swedish Hockey League were diagnosed with having concussion using guidelines recommended by the International Conference on Concussion in Sport [7,36]. Of these concussed players, three experienced unconsciousness and 15 experienced post concussive symptoms (PCS) lasting greater than six days post injury [36]. In these athletes T-tau and S100B were shown to have an AUC of 0.80 and 0.67, respectively, in diagnosing concussion when T-tau and S100B levels were measured one-hour post injury and compared to T-tau and S100B levels measured in non-matched ice hockey players following a friendly game with no incident of concussion injury [36].

In another study football, soccer, basketball, and ice hockey male and female players affiliated with either the Ludwig Maximilians University in Munich, Germany, or the University of Rochester or Rochester Institute of Technology in Rochester, New York were used to

determine the efficacy of S100B to diagnose concussion [46]. Seventeen athletes were diagnosed with concussion using the Sport Concussion Assessment Tool 2 (SCAT2) and had their S100B serum levels measured three hours post injury [46]. In these athletes S100B was shown to have an AUC of 0.904 in diagnosing concussion when S100B levels were measured three-hours post-concussion and compared to S100B levels measured in non-matched ice hockey players following non-contact ice-hockey skating drills [46].

Future studies must continue to examine the efficacy of these biomarkers using matched pre-season and post-concussion biomarker levels. There must also be a focus on the timing of peak serum concentrations as the time of blood collection post injury may affect biomarker efficacy. Biomarkers that have a high AUC within one hour of concussion injury will be the most useful for side-line assessment.

Prognostic Biomarkers

The biomarkers T-tau, Tau-A, and SNTF may be useful in determining RTP as these biomarkers have been shown to increase following concussion and then decrease as post concussive symptoms are resolved [36,37,39]. Future studies must continue to measure biomarkers following concussion injury to determine if they can be used as prognostic measures of concussion injury. A biomarker that can be used to determine RTP would greatly assist physicians, certified athletic trainers, and coaches in making the difficult decision of when an athlete is ready to RTP following concussion injury.

Conclusion

Since the end of the 20th and beginning of the 21st century, research into the use of biomarkers to diagnose and assess sports-related concussion injury has been gaining in popularity with studies increasing in complexity and improved study design. Currently, T-tau and S100B appear to have the greatest diagnostic potential with T-tau having an AUC of 0.80 one hour after concussion and S100B having an AUC of 0.904 three hours after concussion. Research on concussion biomarkers must continue to be supported by sports players, coaches, and funding organizations so a reliable tool can be generated to predict, diagnose, and monitor return to play in regard to sport concussion injury. Finding a biomarker or biomarkers that assess concussion injury will greatly improve the safety of players, especially those participating in contact sports, by preventing acute and permanent brain damage while at the same time making the diagnosis of concussion by health professionals unambiguous.

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