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Potential Blood-Based Biomarkers for Concussion

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Abstract

Mounting research in the field of sports concussion biomarkers has led to a greater understanding of the effects of brain injury from sports. A recent systematic review of clinical studies examining biomarkers of brain injury following sports-related concussion established that almost all studies have been published either in or after the year 2000. In an effort to prevent CTE and long-term consequences of concussion, early diagnostic and prognostic tools are becoming increasingly important; particularly in sports and in military personnel, where concussions are common occurrences. Early and tailored management of athletes following a concussion with biomarkers could provide them with the best opportunity to avoid further injury. Should blood-based biomarkers for concussion be validated and become widely available, they could have many roles. For instance, a point-of-care test could be used on the field by trained sport medicine professionals to help detect a concussion. In the clinic or hospital setting, it could be used by clinicians to determine the severity of concussion and be used to screen players for neuroimaging (CT and/or MRI) and further neuropsychological testing. Furthermore, biomarkers could have a role in monitoring progression of injury and recovery and in managing patients at high risk of repeated injury by being incorporated into guidelines for return to duty, work or sports activities. There may even be a role for biomarkers as surrogate measures of efficacy in the assessment of new treatments and therapies for concussion.

Keywords

Biomarkers; concussion; mild traumatic brain injury; diagnosis; blood test

Introduction

Concussion is under the umbrella of mild traumatic brain injury (MTBI) and is typically used to describe MTBI in athletes. It has been suggested that sports-related concussions are associated with less disability and more rapid recovery than are concussions in non-athletes. However, neuroimaging suggest similar patterns of neuronal disruption for sports and non-sport related MTBI.¹ Athletes are more vulnerable to the deleterious long-term effects of MTBI because they are often subjected to repetitive trauma and greater levels of physical

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exertion during recovery.¹ Furthermore, there is a tremendous motivation among athletes to return to play. As a result, athletes often underreport symptoms and prematurely return to their regular activities, and may create the impression that they recover more quickly than they actually do.¹ Accordingly, objective diagnostic tools would be invaluable in this setting.

The diagnosis of concussion or MTBI can be elusive because it is not always evident on physical exam. The diagnosis of concussion acutely after a head trauma depends on a variety of measures, including neurological examination, neuropsychological evaluation and neuroimaging. Neuroimaging techniques such as computed tomographic scanning (CT scan) and magnetic resonance imaging (MRI) are used to provide objective information.² However, CT scanning has low sensitivity to diffuse brain damage and confers exposure to radiation. MRI can provide information on the extent of diffuse injuries but its widespread application is restricted by cost, availability and its yet undefined role in management of MTBI.³ Moreover, conventional neuroimaging techniques and neuropsychological tests often fail to adequately detect injury, in particular, the recognition of diffuse axonal injury (DAI), also known as traumatic axonal injury.⁴ There are promising new neuroimaging techniques being examined that include functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET).⁵⁻¹⁷ However, the role of these techniques in the clinical management of concussion has not been established yet.¹⁸

Role of Biomarkers in Concussion

There is a mounting body of research supporting the use of biomarkers to detect concussion in children and adults, particularly in the last decade.¹⁹⁻²² A recent systematic review of clinical studies examining biomarkers of brain injury following sports-related concussion established that all studies have been published either in or after the year 2000.¹⁹ There have been eleven distinct biomarkers measured in over a dozen studies and S100 β was the most frequently assessed, followed by glial fibrillary acidic protein (GFAP), neuron specific enolase (NSE), Tau, neurofilament light protein (NFL) and amyloid protein.¹⁹ Brain-derived neurotrophic factor (BDNF), creatinine kinase (CK) and heart-type fatty acid binding protein (h-FABP) have also been studied.¹⁹

Early and tailored management of athletes following a concussion with biomarkers could provide them with the best opportunity to avoid further injury. Should serum biomarkers for concussion be validated and become widely available, they could have many roles. For instance, a point-of-care test could be used on the field by trained sport medicine professionals, such as athletic trainers, coaches and clinicians, to help detect a concussion. In the clinic or hospital setting it could be used by clinicians to determine the severity of concussion and be used to screen players for neuroimaging (CT and/or MRI). Furthermore, biomarkers could have a role in monitoring progression of injury and recovery and in managing patients at high risk of repeated injury by being incorporated into guidelines for return to duty, work or sports activities. There may even be a role for biomarkers as surrogate measures of efficacy in the assessment of new treatments and therapies for concussion.

Only recently has chronic traumatic encephalopathy (CTE) come to public attention due findings on autopsy in high profile athletes.^{23, 24} Chronic traumatic encephalopathy (CTE) is a term used to describe clinical changes in cognition, mood, personality, behavior, and/or movement (gait, tremor) occurring years following concussion.^{25, 26} CTE has been found to occur in football, hockey, soccer, professional wrestling, boxing, in military personnel and in victims of physical abuse.^{26, 27} In an effort to prevent CTE and long-term consequences of concussion, early diagnostic and prognostic tools are becoming increasingly important; particularly in sports and in military personnel, where concussions are common occurrences.

Biomarkers for TBI can be classified according to their presence and abundance in specific neuroanatomic structures of the central nervous system such as the astroglia, the neuron cell body, the axon, and the pre/post-synaptic terminals (Figure 1). Biomarkers of injury may also include inflammatory, coagulopathic or vascular markers. The focus of this review will be on biochemical markers that are known to be released specifically from brain after injury.

BIOFLUID BIOMARKERS OF ASTROGLIAL INJURY

S100 β

Perhaps one of the best studied biomarkers of brain injury and concussion in adults and children is S100 β (beta).^{19, 20, 28} S100 β is a calcium binding protein found in astrocytes that helps to regulate intracellular levels of calcium and is considered a marker of astrocyte injury. Though it has shown the ability to detect brain injury, it is not brain specific and can be found in non-neural cells such as adipocytes, chondrocytes, and melanocytes.^{29, 30}

The clinical value of S100 β in MTBI and concussion is shrouded in controversy. A number of studies have found correlations between elevated serum levels of S100 β and CT abnormalities in adults and children.^{20, 31} Unfortunately, its utility in the setting of multiple trauma remains controversial because it is also elevated in trauma patients with peripheral trauma without direct head trauma.^{32, 33} Several studies have found increased serum levels of S100 β in the absence of head injury in soccer players and marathon runners, and individuals participating in vigorous exercise.^{19, 28, 34, 35}

Elevated serum S100 β levels have been associated with increased incidence of post-concussive syndrome and impaired cognition following MTBI.^{36, 37, 38} Accordingly, there are reports that serum levels of S100 β are associated with MRI abnormalities and with neuropsychological examination disturbances.^{39–41} However, there are also a number of studies negating these findings.^{4, 34, 42, 43}

The association between headers in soccer players and S100 β has been assessed in a number of studies.^{34, 35, 44–47} In the article by Otto et al. twelve soccer players performed twenty controlled headers and showed no rise in S100 β protein levels. Similarly, controlled headers in studies by Mussack and Zetterberg, produced insignificant elevations in S100 β .^{44, 47} However, these headers were performed in a controlled setting where the ball was dropped from a specified height and always impacted the forehead. This is in contrast to a competitive match in which the ball may be travelling faster and with greater force, and may not impact the head on the forehead. Accordingly, Stalnacke et al. measured S100 β during

actual soccer matches and found that S100 β levels increased significantly after a game and also correlated with the number of headers.^{45, 46} The clinical significance of this protein elevation does not appear to affect concussion assessment test scores.³⁴

The timing of S100 β of measurement is also important. A recent study by Shahim et al. assessed S100 β in professional ice hockey players pre-season and post-concussion at 1, 12, 36, and 144 hours. S100 β peaked within the first hour, but was only significantly higher at 1-hour after concussion compared to pre-season.⁴⁸ Amateur boxers have slightly elevated levels of S100 β in CSF samples obtained by lumbar puncture after a bout but not long-term.⁴⁹

The technique for analyzing S100 β is another substantial contributor to discrepancies in results from different studies.^{50, 51} When serum S100 β levels from the Liaison Sangtec 100™ (enzyme-linked immunosorbent assay) were compared to the Elecsys S100™ (Roche Diagnostics, Mannheim, Germany), the S100 β concentrations were different between the two immunoassays.⁵⁰

Glial Fibrillary Acid Protein (GFAP)

Glial Fibrillary Acidic Protein (GFAP) is a promising brain-specific glial-derived biomarker for MTBI in adults and children.^{4, 32, 33, 52–55} GFAP is released into serum following a MTBI within an hour of injury and remains elevated for several days after injury.^{33, 52, 55} Unlike S100 β , GFAP is elevated in MTBI patients with axonal injury as evidenced by MRI at 3 months post-injury.⁴ In adults and children, serum GFAP levels distinguish MTBI patients from trauma patients without TBI and detect intracranial lesions on CT with a sensitivity of 94%–100%.^{32, 33, 52, 54} Moreover, GFAP out-performs S100 β in detecting CT lesions in the setting of multiple trauma when extracranial fractures are present.^{33, 54} GFAP also predicts the need for neurosurgical intervention in patients with MTBI.^{52, 55}

Although GFAP has been studied in brain injury since the 1990's, it is not until recently that it has been assessed in serum following trauma^{4, 33, 52, 53, 55} and more specifically in children^{32, 54} and in sports.^{49, 56–58} The performance of GFAP has been much better (more accurate in detecting injury) in trauma patients presenting with MTBI to the emergency department compared to the studies performed in athletes to-date. This discrepancy may stem from the timing of the blood draws relative to time of injury or from the type of assay used.⁵⁵ In studies with trauma patients, samples have been drawn within 4–6 hours^{32, 33, 52, 54, 55} and up to 24 hours after injury.^{4, 53} However, in athletes, the samples tend to be drawn later from days to months.^{57, 58} The CSF of 30 Olympic boxers and 25 non-boxing matched controls were measured within 6 days after a bout and again after a rest period of at least 14 days and both GFAP and S100 β concentrations were significantly increased after boxing compared to controls. However, GFAP (but not S100 β) concentrations remained elevated after the rest period. This underscores the importance of understanding the temporal profile of the biomarkers being applied in studies.⁵⁵

BIOFLUID BIOMARKERS OF NEURONAL INJURY

Neuron Specific Enolase (NSE)

Neuron specific enolase (NSE) is one of the five isozymes of the glycolytic enzyme enolase found in central and peripheral neuronal cell bodies and it has been shown to be elevated following cell injury.⁵⁹ It is also present in erythrocytes and endocrine cells and has a biological half-life of 48 hours.⁶⁰ This protein is passively released into the extracellular space only under pathological conditions during cell destruction. Several reports on serum NSE measurements of mild TBI have been published.^{59, 61–64} Many of these studies either contained inadequate control groups or concluded that serum NSE had limited utility as a marker of neuronal damage. Early levels of NSE and MBP concentrations have been correlated with outcome in children, particularly those under 4 years of age.^{65–68} A limitation of NSE is the occurrence of false positive results in the setting of hemolysis.^{69, 70}

Zetterberg et al. measured S100 β and NSE after 2 months of nonparticipation in boxing and found that NSE showed a prolonged decay in boxers who were exposed to very frequent, repetitive head trauma during most of the year.^{58, 71} In two studies led by Stalnacke et al. blood samples were obtained before and after competitive games and found that both S100B and NSE were increased after the game. NSE was not related to the number of headers and other trauma events but S100B was.^{46, 72} In contrast, in Shahim's study of hockey players pre-season and up to 144 hours post-concussion NSE remained at pre-season levels and was not significantly elevated at any time-point after concussion.⁴⁸

Ubiquitin C-terminal Hydrolase (UCH-L1)

A promising candidate biomarker for MTBI currently under investigation is Ubiquitin C-terminal Hydrolase-L1 (UCH-L1).^{53, 55, 73, 74} UCH-L1 was previously used as a histological marker for neurons due to its high abundance and specific expression in neurons.⁷⁵ This protein is involved in the addition and removal of ubiquitin from proteins that are destined for metabolism.⁷⁶ It has an important role in the removal of excessive, oxidized or misfolded proteins during both normal and pathological conditions in neurons.⁷⁷ Clinical studies in humans with severe TBI have confirmed, using ELISA analysis, that the UCH-L1 protein is significantly elevated in human CSF^{78–80} and is detectable very early after injury. It remains significantly elevated for at least 1 week post-injury.^{79, 80} Studies in severe TBI patients have demonstrated a very good correlation between CSF and serum levels.⁸¹ Increases in serum UCH-L1 have also been found in children with moderate and severe TBI.⁸²

Notably, elevated levels of UCH-L1 are detectable in the serum of MTBI patients within an hour of injury and appear to discriminate concussed patients from uninjured and non-head injured trauma control patients (orthopedic injuries or motor vehicle trauma without head trauma).^{55, 73} A handful of studies have shown serum UCH-L1 levels to be significantly higher in those with intracranial lesions on CT than those without lesions^{53, 55, 73, 74} and to be much higher in those eventually requiring a neurosurgical intervention.^{55, 73}

BIOFLUID BIOMARKERS OF AXONAL INJURY

Alpha-II Spectrin Breakdown Products

Alpha-II-spectrin (280 kDa) is the major structural component of the cortical membrane cytoskeleton and is particularly abundant in axons and presynaptic terminals.^{83, 84} It is also a major substrate for both calpain and caspase-3 cysteine proteases.^{85, 86} A hallmark feature of apoptosis and necrosis is an early cleavage of several cellular proteins by activated caspases and calpains. A signature of caspase-3 and calpain-2 activation is cleavage of several common proteins such as cytoskeletal α II-spectrin.^{87, 88} Levels of spectrin breakdown products (SBDP's) have been reported in CSF from adults with severe TBI and they have shown a significant relationship with severity of injury and clinical outcome.^{80, 89–95} The time course of calpain mediated SBDP150 and SBDP145 (markers of necrosis) differs from that of caspase-3 mediated SBDP120 (marker of apoptosis). Average SBDP values measured in CSF early after injury have been shown to correlate with severity of injury, CT scan findings and outcome at 6 months post injury.⁹⁶

Serum SBDP145 has also been measured in serum in children with TBI. Levels were significantly greater in subjects with moderate and severe TBI than in controls (but not in mild TBI) and were correlated with dichotomized GOS at 6 months.⁸² This correlation did not hold true for mild TBI. More recently, however, serum levels of SBDP150 have been examined in patients with MTBI and have shown a significant association with acute measures of injury severity, such as GCS score, intracranial injuries on CT and neurosurgical intervention.⁹⁷ In this study, serum SBDP150 levels were much higher in patients with mild TBI/concussion than other trauma patients who did not have a head injury.⁹⁷

Alpha-II Spectrin N-terminal fragment (SNTF) is an approximately 150-kDa NH₂-terminal fragment (NTF) of α -spectrin that is cleaved by calpain through proteolysis. SNTF is increased in human blood after severe TBI⁷⁸ and has been shown to correlate with cognitive impairment after 3 months following MTBI.⁹⁸ In a small pilot study, SNTF plasma levels were detectable in MTBI patients within 24 hours of injury and corresponded with significant differences in fractional anisotropy and the apparent diffusion coefficient in the corpus callosum and uncinate fasciculus measured by DTI.⁹⁸ Elevated levels of SNTF have also been associated with the development of post-concussion symptoms in professional hockey players.⁹⁹ Compared to players who were not concussed, or whose concussion symptoms resolved rapidly, there was an increase of SNTF concentrations from 1 hour up to 144 hours post-concussion in those players experiencing persistent symptoms.⁹⁹

Tau Protein

Following a concussion, axons appear to be most susceptible to damage. Tau protein is an intracellular, microtubule-associated protein that is highly enriched in axons and is involved with assembling axonal microtubule bundles.¹⁰⁰ Tau is an interesting biomarker because cumulative brain damage sustained from single, episodic, or repetitive concussions can provoke the development of a tauopathy (marked accumulation of tau-immunoreactive astrocytes) and chronic traumatic encephalopathy (CTE).^{23, 101} Tau deposits are also found in the brains of individuals with Alzheimer's, although the distribution is different.¹⁰¹

Permanent neurological impairment is a serious concern for athletes who experience repetitive head traumas since both concussive and sub-concussive blows can be significantly damaging.^{18, 101, 102} A recent systematic review showed that biomarkers (such as Tau, GFAP and NSE) can remain elevated even after athletes do not participate in their sport for over 2 months.¹⁹ This prolonged decay can also be seen in boxers even without anamnestic or clinical symptoms of a concussion or traumatic brain injury.^{49, 57, 58, 71}

Tau lesions are related to axonal disruption^{103, 104} and Tau is being investigated as a potential biomarker of CNS injury. There are, however, inconsistencies in the performance of Tau in the form of cleaved-Tau (C-Tau), total-Tau (T-Tau), and phosphorylated-Tau (P-Tau) in the trauma literature. Initial studies assessing Tau in CSF in severe TBI correlated with clinical outcome^{105–110}, however, these findings did not hold true when measured in peripheral blood^{106, 111} or in mild TBI, where Tau was a poor predictor of CT lesions and post-concussion syndrome.^{42, 112–114}

In 2013, Neselius et al. measured Tau in plasma and found significantly increased levels after a bout of Olympic boxing compared to control levels that decreased over time.⁵⁷ These elevations were in boxers who had no symptoms of concussion. Moreover, in 2012, when CSF levels of Tau were examined in this same group of boxers, there were significant increases in Tau but there was no correlation between plasma and CSF-Tau.⁴⁹ Zetterberg et al. found levels of T-Tau in CSF within 10 days of a bout were elevated in both amateur boxers who had received many hits (>15) or high-impact hits to the head as well as in boxers who reported few hits. More recently, a study of professional hockey players showed that serum T-Tau out-performed S-100B and NSE in detecting concussion at 1-hour after injury and that levels were significantly higher in post-concussion samples at all times compared with preseason levels.⁴⁸ T-Tau at 1 hour after concussion also correlated with the number of days it took for concussion symptoms to resolve. Accordingly, T-Tau remained significantly elevated at 144 hours in players with post-concussive symptoms (PCS) lasting more than 6 days versus players with PCS for less than 6 days.⁴⁸

The inconsistencies in all these studies are multifactorial and include variability in the Tau assays used (differing sensitivities and specificities), variability in the type and measurement of outcomes, and the timing of the sample collection.

Neurofilaments

Neurofilaments are heteropolymeric components of the neuron cytoskeleton that consist of a 68 kDa light neurofilament subunit (NFL-L) backbone with either 160 kDa medium (NFL-M) or 200 kDa heavy subunit (NFL-H) side-arms.¹¹⁵ Following TBI, calcium influx into the cell contributes to a cascade of events that activates calcineurin, a calcium-dependent phosphatase that dephosphorylates neurofilament side-arms, presumably contributing to axonal injury.¹¹⁶ Neurofilament medium polypeptide (NFL-M) protein was evaluated in the CSF and serum of healthy individuals and patients with stroke and mild-to-severe TBI. NFL-M was increased in patients with stroke and TBI and 44% of patients with MTBI had increased NFL-M concentration that was significantly higher in patients with polytrauma.¹¹⁷

Phosphorylated NFL-H has been found to be elevated in the CSF of adult patients with severe TBI compared to controls.⁷⁸ Similarly, hyperphosphorylated NFL-H has also been correlated with severity of brain injury in children.¹¹⁸ In a study by Zurek et al. NFL-H levels taken on the 2nd to 4th day remained significantly higher in patients with poor outcome in comparison to patients with good outcome. Additionally, NFL-H was significantly higher in those children with diffuse axonal injury on initial CT scan.¹¹⁸ Accordingly, Vajtr et al. compared 10 patients with DAI/TAI to 28 patients with focal injuries and found that serum NFL-H was much higher in patients with DAI/TAI over 10 days after admission. Serum NFL-H levels were highest from the fourth to the tenth 10th day in both groups.¹¹⁹ In a small pilot study of MTBI patients, Phosphorylated NFL-H (pNFL-H) levels were higher in MTBI patients compared to healthy controls and were elevated in subjects with positive CT scans when measured on Day 1 after injury but not on Day 3.¹²⁰

NFL-L has also been shown to be elevated in amateur boxers with MTBI following a bout when measured in CSF after lumbar puncture.^{49, 58} The levels were associated with the number of hits to the head received, as well as subjective and objective estimates of the intensity of the fight.⁵⁸ Furthermore, NFL remained elevated after a rest period of at least 14 days in a subgroup of boxers.^{49, 121}

Future Directions

Mounting research in the field of sports concussion biomarkers has led to a greater understanding of the effects of brain injury from sports. Moving forward, there are many challenges to consider and overcome as we continue to pursue the clinical application of brain-specific blood-based biomarkers in sports. Firstly, biomarkers should be compared to reliable and objective measures of concussion. It is difficult to rate the predictive power of a biomarkers if the clinical measures they are being compared against are subjective and variable. For instance, biomarkers could be compared to novel neuroimaging techniques and/or to validated clinical tools and combined with them (neuroimaging, clinical tools) to improve diagnostic and prognostic accuracy. Secondly, common clinical and biomarker-related data elements need to be consistently applied to future studies on sports concussion, as they are currently being employed for all severities of TBI, including the type and timing of assessments.^{122, 123} Thirdly, each study should describe the accuracy, precision, specificity, detection limit, quantitation limit, linearity, and range of the biomarker assay/platform being assessed. Additionally, the different assays being used to measure the same biomarker in distinct studies should be compared and contrasted.⁵⁰ Finally, sample collection for biomarker measurement will need to span longitudinally over multiple time-points in order to assess their time course.^{48, 55} The temporal profiles, in turn, will be useful for determining optimal times to measure levels of these markers after concussion and for guiding return-to-play decisions. As part of this, the timing of outcome measures relative to the timing of the biomarkers needs to be carefully considered in the design of future studies.

Conclusion

The studies reviewed assessing potential biomarkers for TBI, and more specifically concussion, are promising and could provide clinicians and trained sport medicine

professionals with diagnostic, prognostic, and monitoring information on recovery. Tailored and timely management of athletes following a concussion would provide them with the best opportunity to avoid further injury. Individuals with concussion are acutely at risk for bleeding and axonal injury and long-term, can suffer impairment of physical, cognitive, and psychosocial functioning. With the growing incidence of chronic traumatic encephalopathy among athletes, strategies that reduce the risk of becoming injured would be invaluable. Diagnostic tools, such as blood-based biomarkers, that could detect injuries promptly need to be pursued rigorously. Future studies will require uniform and robust research methodology, larger sample sizes, a description of the characteristics and precision of the biomarkers being examined, as well as reliable and objective outcome measures.

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Figure 1.

Picture of the neuron and the neuroanatomic locations of potential TBI biomarkers. S100 β is the major low affinity calcium binding protein in astrocytes that helps to regulate intracellular levels of calcium. Glial Fibrillary Acidic Protein (GFAP) is a monomeric intermediate protein found in astroglial skeleton that is found in white and gray brain matter and is strongly upregulated during astrogliosis. Neuron specific enolase (NSE) is one of the five isozymes of the glycolytic enzyme enolase found in central and peripheral neuronal cell bodies. UCH-L1 is highly abundant in neurons and was previously used as a histological marker for neurons. Alpha-II-spectrin is the major structural component of the cortical membrane cytoskeleton and is particularly abundant in axons and presynaptic terminals. Tau is an intracellular, microtubule-associated protein that is highly enriched in axons. Neurofilaments are heteropolymeric components of the neuron cytoskeleton. (Taken from Papa, L.: Exploring Serum Biomarkers for Mild Traumatic Brain Injury. In: Brain Injury Principles: Molecular, Neuropsychological, and Rehabilitation Aspects in Brain Injury Models. Kobeissy F. [ed]: CRC Press/Taylor & Francis, 2015, Figure 22.1, p 303)