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An Examination of the Correlation between Advancements in TBI Research and the Long-Term Health Outcomes of High-Risk Populations: The Use of Biomarkers *vs.* Symptom Assessment

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Abstract

Historically, assessment for Traumatic Brain Injury (TBI) has been dependent on the subjective collection of self-reported symptoms. However, developments in neurophysiology have identified unique biomarkers that correlate with concussive injury and imaging modalities that allow for visualization of changes to the Blood Brain Barrier (BBB). This review will examine the utility of these novel identifiers as an objective option for acute evaluation and their potential contribution to treatment planning.

Keywords: Brain injury; Neurophysiology; Blood brain barrier; Treatment

Introduction

As the medical community continues to learn more about the impact of trauma on the brain, those professions whose members are most at risk must continually evolve their standards for prevention, detection and treatment of brain injuries. Of those at-risk professions, two of the most prominent are the athletic and military communities.

Consequently, both are prime sources for study when it comes to the evolution of TBI diagnosis and treatment and the long-term benefits that improvements in care can confer to affected individuals [1].

A potential source for the advancement of diagnostic and treatment procedures is the discovery of biomarkers that, when dysfunctional, correlate with acute concussion.

While assessment of symptoms has traditionally been the manner by which TBI was diagnosed, these markers have the potential to stage where in the recovery process the injured individual stands at any given point, as well as predict a timeline for return to baseline. Current guidelines for TBI diagnosis include a non-specific combination of confusion, disorientation, impaired consciousness, memory loss and lack of structural damage on imaging. Consequently, the ability to definitively determine TBI recovery has the potential to prevent compounding trauma by clearly delineating a traumatic incident and its resolution [2].

Nevertheless, in the process of pursuing a more objective means of assessment based in neurophysiology, the value of neurocognitive evaluation and self-reported symptoms cannot be completely dismissed. Albeit subjective, symptomatic assessments remain the primary method of point of care evaluation. While biomarkers are a promising development in the field of TBI assessment, they are still very much in a laboratory testing phase rather than an acute diagnostic modality. However, the more the hypothesis of a correlation between unique biologic identifiers and clinical evidence of concussion resists further challenges, the more these biomarkers can be used to help determine treatment plans and prevent eager athletes and service members from returning to exposure environments before fully healed. This is especially important given the exponentially negative effect successive insults have on an injured brain. Repetitive impacts have been shown to induce protracted cognitive, motor and behavioral deficits. Thus, the adoption of an objective means of assessment must be considered as it becomes available.

Inclusion criteria for this study was based on the exposure risk of potential subjects. Therefore, all articles focus on or address to some degree, NCAA and/or professional athletes and/or military members. The oversight agencies of these professions include the NCAA and the department of defense, who are responsible for producing the guidelines that govern subjects' diagnosis and treatment. Material is also included that addresses the medical community's concern regarding the exposure risk for members of these professions [3].

Information was sourced from frontiers in neurology, biomedical engineering society, springer nature and clinical journal of sports medicine. The search was progressively narrowed from TBI to repetitive TBI to repetitive TBI among at-risk professions (military, athletes) to objective assessments of TBI (biomarkers, scans). Studies were selected that could evaluate the value of objective assessment strategies compared against self-reported and symptomatic diagnoses. Literature ultimately included for review is as follows:

- Defining acute traumatic encephalopathy: Methods of the "HEAD Injury Serum Markers and Multi-Modalities for Assessing Response to Trauma" (HeadSMART II) study.
- Proteomic profiling of plasma biomarkers associated with return to sport following concussion: Findings from the NCAA and department of defense care consortium.
- Quantitative imaging of blood-brain barrier permeability following repetitive mild head impacts.
- Time delta head impact frequency: An analysis on head impact exposure in the lead up to a concussion: Findings from the NCAA-DOD care consortium.
- Quantifying the value of multidimensional assessment models for acute.

Literature Review

Defining acute traumatic encephalopathy: Methods of the "HEAD Injury Serum Markers and Multi-Modalities for A ssessing Response to Trauma" (HeadSMART II) study

TBI has largely been considered a syndromic diagnosis; however, when there exists the possibility of sub-clinical impacts, whose symptoms may be variable or nebulous, but may still manifest in persistent neuropsychiatric consequences, then this suggests that there is a need for objective assessment measures to fully understand. The (HEAD Injury Serum Markers and Multi-Modalities for Assessing Response to Trauma) HEADSmart II study performed by Peacock et. al, explores the applicability of biomarkers and neurocognitive testing as a physiologic basis for diagnosis of Acute Traumatic Encephalopathy (ATE). The BRAINBox TBI test utilizes both blood protein biomarkers and clinical assessments for pathological and neurocognitive impairments. These injury serum markers and multiple modalities of assessment offer the possibility for *in vitro* diagnosis for TBI, even at the subclinical level. Thus, it may also be predictive for identifying patients who are at risk of developing post-concussive symptoms [4].

Few objective tests are available to detect injury and predict dysfunction when imaging is negative; regardless of normal imaging, patients can still present with symptoms of TBI. In a study of ED physicians, clinical prediction of which patients would display TBI symptoms within 90 days of a mild injury was only 8.1% sensitive and 54.5% specific. Thus, Peacock et al. hypothesize that the shortcoming of clinical diagnosis is the solely symptomatic nature of diagnosis for a condition where symptoms are vague, physical signs nonspecific and the reliability of medical history varies widely. ATE diagnosis using biomarkers adds the objective evidence of brain derived proteins, detectable in the blood, resulting from injury-related leakage, to the diagnostic arsenal. Though this method of testing for ATE is not currently available for point of care use, adoption of this method of assessment would result in TBI being defined as having abnormal biomarkers and/or neurocognitive dysfunction with either normal or abnormal imaging. The second primary aspect of the multi-modality HEADSmart assessment is the neurocognitive evaluation. Identifying TBI in those with mild symptoms ensures proper treatment, thus having the potential to improve patient outcomes.

The BRAINBox TBI test, as part of an objective diagnosis of ATE, includes a proprietary serum/plasma biomarker assay, the most notable of which are GFAP (glial fibrillary acidic protein), NSE (Neuron Specific Enolase-2), NRGN (neurogranin), SNCB (beta-synuclein), MT3 (metallothienein-3). These biomarkers were included because the HEADSMART pilot trial indicated that they might have predictive value based on the trial's statistical algorithms. Additionally, a digital neurocognitive assessment was performed at each visit for study participants. Those to be included in the ATE cohort were determined by a Diagnostic Adjudication Committee (DAC) based on expert clinical examination of de-identified medical records, physical exam notes, neurological assessment and imaging reports. The DAC was blinded to BRAINBox test results [5].

Data collected using the multi-modality approach of biomarkers, clinical characteristics, neurocognitive and neuropsychological assessments, yielded three models for predicting symptomatic status in ATE patients. In order to evaluate its performance as a prognostic tool, baseline demographics at the index visit were included and models were designed to assign high or low risk for symptoms at the 14, 30 and 90 day visits. The validation phase of the assessment examined possible confounding variables (age, sex, time from injury to blood draw). Upon validation, the model would provide clinicians with both a diagnostic tool for ATE and an objective predictor for risk of post-concussive symptom presentation.

Proteomic pro iling of plasma biomarkers associated with return to sports following concussion: Findings from the NCAA and department of defense care consortium

Vorn et al. further explore the pathophysiological mechanism in neurobiological recovery, examining plasma biomarkers in the context of the NCAA-DoD Concussion Assessment, Research and Education (CARE) consortium and their findings regarding Sports Related Concussion (SRC). The multiplexed proteomic technique utilized targeted 1,305 proteins in plasma samples using DNA aptamers. The inclusion criteria requires that blood be collected within 48 hours of injury. Concussed individuals are then tracked until asymptomatic and divided into recovery <14 days and recovery ≥ 14 days cohorts. The protein assay identified 87 dysregulated plasma proteins, 32 upregulated and 55 dysregulated in recovery ≥ 14 days compared to the recovery <14 days cohort [6].

Dysregulated proteins were analyzed using Ingenuity Pathway Analysis (IPA) software. Analysis revealed associations with the STAT3 pathway, regulation of the epithelial mesenchymal transition by growth factors pathways and acute phase response signaling. Analysis of the biomarkers in peripheral circulation following SRC provides insight into the intrinsic factors influencing mechanism of injury and symptomatic presentation.

Serum Glial Fibrillary Acidic Protein (GFAP) and Ubiquitin c-terminal Hydrolase L1 (UCH-L1) were found to be elevated in cases of concussion and the degree of elevation was found to correlate to the severity of injury. GFAP and tau specifically were associated with recovery ≥ 14 days, thus suggesting the utility of inflammatory cytokine levels as prognostic markers for recovery. Further evidence supporting this hypothesis is that elevated interleukin (IL) 1 and IL-6 within 6 hours of injury correlates to extended symptom duration. Conversely, plasma monocyte chemoattractant protein-1 and 4 are associated with the recovery phasex. Of note, the identification of protein changes that denote acute SRC and recovery timeline are hypothesis driven, thus restricting the identification of unique biomarkers. The SOMAscan assay used by Vorn et al. measures >1000 proteins, thereby accelerating the discovery of potentially unique biomarkers with the potential to characterize the relationships in greater depth.

In addition to the SOMAscan of the blood plasma sample collected within 48 hours of injury, the 140 concussed athletes meeting the US department of defense definition of concussion based on evidence-based guidelines were evaluated using the Sport Concussion Assessment Tool-Third edition (SCAT-3), the Standardized Assessment of Concussion (SAC), the Balance Error Scoring System (BESS) and the Brief Symptom Inventory 18 (BSI-18). This additional data supports the legitimacy of the clinical diagnoses, as well as the correlation of clinical diagnoses with biomarker dysregulation [7].

The 87 plasma proteins dysregulated in SRC can be discussed as those upregulated in recovery ≥ 14 days and those downregulated in recovery ≥ 14 days. Those upregulated include: Haptoglobin (HP), Leptin (LEP), Apolipoprotein B-100 (APOB), Tyrosine kinase 2 (TYK2), Advanced Glycosylation End Product-Specific Receptor (AGER) and IL36A. Those downregulated include: Erythrocyte Membrane Protein Band 4.1 (EPB41), protein S100-A12 (S100A12), WNK lysine deficient protein kinase 3 (WNK3), ATP synthase subunit beta, mitochondrial (ATP5B) and Epidermal Growth Factor (EGF). The top 30 dysregulated proteins, including those listed above, were analyzed *via* IPA to look for molecular mechanisms associated with prolonged recovery.

The canonical recovery pathways of greatest significance were the Signal Transducer and Activator of Transcription 3 (STAT3) pathway, tumor microenvironment pathway, regulation of the epithelial mesenchymal transition by growth factors pathway and acute phase response signaling. Mechanistic analysis showed protein-protein interaction in hepatic system development and function, cellular movement and organismal injury and abnormalities networks. Of these pathways, the most significant protein dysfunctions were associated with the STAT3 pathway, suggesting a proinflammatory mechanism. Vascular injury markers were also identified, including Vascular Endothelial Growth Factor C (VEGFC), VWF, Platelet Derived Growth Factor Receptor Alpha (PDGFRA) and FN1 proteins. The SRC-related disruption to the BBB, leading to increase of peripheral protein levels and immune cells and proteins recruited to the site of the injury, is supportive of the proinflammatory influence on prolonged SRC recovery. However, it also suggests the possibility of BBB damage in concussed athletes, which is examined by Leaston et al. using animal models [8].

Quantitative imaging of blood-brain barrier permeability following repetitive mild head impacts

Leaston et al. looked at the early pathology and effect of repetitive mild concussive forces to a closed head on the BBB, as compared to the pre-impact brain, using a new imaging modality, Quantitative Ultrashort Time-to-Echo Contrast Enhanced (QUTE-CE). BBB permeability was measured at baseline and within 1 hour of impact. Functional imaging revealed even a mild concussive force applied to the closed head of a rat measurably increased BBB permeability. This increase was more significant after second and third impacts respectively, with the affected regions being the prefrontal cortex, basal ganglia, hippocampus, amygdala and brainstem.

The failure in the BBB, to which cerebrovascular dysfunction can be attributed, most commonly occurs in moderate to severe TBI and may contribute to the development of neurodegenerative disease. Although 75% of all TBIs are the result of mild head impacts, these injuries too must still be given sufficient time to resolve before further insult is introduced. When not addressed properly, ATE can morph into Chronic Traumatic Encephalopathy (CTE), with long-lasting cognitive, motor and behavioral deficits. QUTE-CE imaging addresses the need for non-invasive, quantitative, whole brain assessment of BBB leakage.

In the protocol used by Leaston et al., animals were scanned to establish baseline BBB permeability prior to any head trauma. They were then subjected to mild impacts every 24 hours for 3 cycles and imaged within 1 hour of each insult. Fixation and post-mortem histology were then performed. Quantification of BBB permeability was obtained *via* analysis of the slope for the CBV *vs.* time curve and modulations in BBB permeability were calculated using percentage change in apparent CBV per second. On histology, increased FTC permeability in the perivascular space denotes increased BBB permeability, quantified by analyzing the intensity of FITC-dextran fluorescence outside of the vasculature. These findings provide validation for the findings on QUTE-CE imaging [9].

Increased permeability was reliably found near the site of impact, most commonly in the orbital and motor cortex, compared to relatively low permeability in the substantia nigra. Using heat maps, sites of increased BBB permeability are shown in the sagittal view to begin in the forebrain (prefrontal cortex, anterior olfactory tubercles) and extend caudally (retrosplenial cortex, colliculi, pons). While BBB damage always affected the olfactory system and striatum, hindbrain injury was less consistent. Coronal sections show lateralization and increased permeability of BBB with second impact. Permeability progresses from 2% on day 1 to 7% on day 2 and 19% on day 3.

Though the permeability pattern was consistent, variance between individual subjects was evident in the degree of BBB resilience to traumatic force. While some subjects displayed significant increase in permeability after the first impact, others remained at or near baseline until imaged after sustaining multiple impacts. Ultimately, though a single mild impact resulted in only a modest increase in permeability, subsequent second and third impacts resulted in more severe and

widespread damage to the BBB, causing increased degree of permeability and a greater area being affected.

In cases where symptoms resolved within 24 hours, use of the apparent diffusion coefficient as a proxy for the resultant vasogenic edema from BBB permeability showed edema to peak 6 hours after the singular mild insult. Thus, while post-mortem histology is limited by the time from impact to the time of animal sacrifice, QUTE-CE does not face the same limitations. The conclusions reached through imaging with QUTE-CE are supported by Veksler et al., who used DCE MRI to generate maps of BBB permeability in American football players. These showed increased BBB permeability in American football players compared to a control group of athletes from non-contact sports. Moreover, the post-impact elevation in BBB permeability persisted for months after contact [10].

Leaston et al. show that even a single mild impact can increase BBB permeability and repetitive insult intensifies vulnerability and diffuses it distally. QUTE-CE imaging also revealed the variability among individual subjects in sensitivity to traumatic forces applied to a closed head. Nevertheless, BBB leakage consistently peaked after the second impact, highlighting the importance of complete recovery between impacts, especially for individuals with a high likelihood of experiencing a second impact (*i.e.,* pro athletes and military).

Time delta head impact frequency: An analysis on head impact exposure in the lead up to a concussion: Findings from the NCAA-DOD care consortium

The time delta head impact frequency study performed by Seifert et al., further explores the relationship between injury severity and timing between insults. The hypothesis underlying this study is that head impacts resulting in concussion are the product of impact severity, total number of insults and frequency of sub-concussive impacts. The topic of frequency is most extensively investigated, with the metric for frequency given the label “time delta.” Time delta is used to determine if frequency of head impact is greater on the date of the concussion compared to other days during which similar activities were undertaken without resulting in concussion. It accounts for head impact frequency, head impact accrual rate, Risk Weighted Exposure (RWE) and RWE accrual rate.

The proposed mechanism is that impact resulting in SRC is dependent on total number, severity and frequency of head impacts. The cumulative risk is referred to as Risk Weighted Exposure (RWE), calculated with the equation.

$$RWE = \sum \frac{1}{1 + e^{-\left(-10.2 + 0.0433 * \ddot{x} + 0.000873 * \ddot{\theta} - 0.000000920 * \ddot{x} * \ddot{\theta}\right)}}$$

The total head impact burden an athlete acquires over time (HIE) can reduce tolerance, thus the hypothesis for statistical analysis was that HIE frequency would be elevated on the date the athlete sustained the concussion compared to dates when a concussion was not recorded.

Those included in the study cohort were all NCAA division I football players and concussive impact was identified for all SRC’s analyzed. Statistical analysis was performed both inter-and intra-athlete. Linear regression analysis for each contact session revealed a linear correlation between head impact and RWE accumulation rate. On the day of injury, 92% of athletes had significant linear accumulation rate (linear regression p-value<0.05) for head impacts and 85% of athletes had significant linear accumulation rate (linear regression p-value<0.05) for RWE. For every head impact session recorded for the study, 84%of athletes had significant linear accumulation rate (linear regression p-value<0.05) for head impacts and 79% of athletes had significant linear accumulation rate (linear regression p-value<0.05) for RWE. These statistical significances agree with the hypothesis proposed by Seifert et al., and since RWE depends on acceleration magnitude, both the number of impacts and the magnitude of acceleration at the time of impact were elevated on the day of the injury. When looking at intra-athlete comparison, HIE from the injury date was analyzed against the athlete’s own HIE throughout the season, thereby eliminating confounding variables.

Concussion onset during periods of elevated exposure compared to time delta periods where a concussion was not diagnosed suggests a reduction in tolerance during periods of elevated HIE frequency. Furthermore, elevation of HIE frequency and RWE on date of injury implies a combined risk from repeated impacts. Such insight allows for the development of an individualized risk profile accounting for exposure, concussion history, impact magnitude and intrinsic biological susceptibility. Such a profile would allow medical personnel to identify those most at risk and in need of monitoring. Noting the importance of frequency to the combined risk of repeated impacts can then be used in developing a protocol for monitoring cumulative exposure to prevent the concussive incident.

Quantifying the value of multidimensional assessment models for acute concussion: An analysis of data from the NCAA-DoD care consortium

The quantification of the multidimensional assessment models explored by the NCAA-DoD care consortium is first and foremost a statistical modeling approach to evaluating selected standard assessments for acute concussion. The models developed by Garcia et al. attempt to determine which of the multidimensional assessments available has a change score of greater clinical utility than the raw score. Furthermore, they quantitatively evaluate clinical concussion assessment tools under the conditions of limited data or sans objective measures, yielding insight into which standard assessment tools are most effective in acute concussion assessment. In this way, they also produce a singular risk estimate to guide clinical decision making.

As a single measure to guide acute concussion management, multivariate logistic regression models combining multiple assessments, injury characteristics and individual risk modifiers produce the most sensitive analysis of acute concussion symptomaticity. While baseline information improved models’

discriminatory capacity, accurate assessment of acute concussion without this information still reaches clinically acceptable standard. This was as certained by having NCAA athletes undergo baseline assessment and evaluations at the time of injury (<6 hrs), 24-48 hrs post-insult, at the time of asymptomatic presentation, at the time unrestricted Return to Play (RTP) clearance is granted and 6 months post-RTP. SRC diagnoses and RTP decisions were made by local institution's medical staff. These evaluations included concussion risk modifiers (age, sex) and the traditional tools of SAC, SCAT and BESS, the benefit of which is that these tools are widely available and easy to administer on sidelines.

Limited models, eliminating one variable at a time to estimate impact on full multivariate model, were created for every variable included in the full model and analyzed using Python software. The limited model removing the SCAT symptom score from consideration resulted in the most significant decrease in model performance.

Furthermore, objective multivariate models did not consider self-reported symptoms, since symptom under-reporting is a major concern of current concussion management protocols; however, these objective models compared to the full multivariate models displayed decreases in sensitivity, specificity and AUC of 0.34, 0.28 and 0.29 respectively.

Loss in AUC was determined to be statistically significant ($p<0.001$). Conversely, the limited model removing BESS did not see a significant reduction in AUC, implying that SAC and SCAT are more important. Indeed, the best univariate models, measuring only SAC and SCAT, achieved comparable performance to multivariate models, suggesting that the removal of self-reported symptoms from the evaluation is most significantly detrimental to the accuracy of acute concussion assessment and that symptoms are better indicators of acute concussion than neurological evaluations or balance tests.

Others, such as Broglio et al., have found neurocognitive assessments to be of higher sensitivity than an assessment of self-reported symptoms. This is in large part due to symptom underreporting, which is estimated to occur at rates up to 50%. Additional factors to be considered in gauging risk include sex (females are at greater risk than males) and the unique presentation of or resistance to, symptoms between individuals. Since symptom presentation and resilience variability are non-quantifiable metrics, neither were included in this quantitative analysis. Therefore, the potential usefulness of an objective evaluation metric, beyond the clinical capacity of the assessments included in this statistical analysis, cannot be disregarded. Nevertheless, statistical models are important tools in the future development of data-driven concussion assessment strategies and are undeniably useful in concussion management at the sideline level.

Cohort subjects in the modeled data set were assessed at <6 hrs and 24-48 hrs, with separate multivariable logistic regression models created for the <6, 24 and 48 hr time points. The multivariable models produced sensitivity, specificity and area under the curve up to 0.94, 0.97 and 0.99, respectively. The univariable model for SCAT produced the next-most-accurate results when considering all calculated measurements, with 0.93, 0.97 and 0.98 for sensitivity, specificity and area under the receiver operating characteristic curve, respectively. Thus, multivariate models outperformed both objective and univariate models, suggesting that multifactorial assessments should be used. Furthermore, omitting symptoms from the multivariate model to produce an objective model decreased discrimination ability, the conclusion of which is that self-reported symptoms are important to the assessment of acute injury. With symptomatic assessments being the most effective tools in acute concussion assessment, the inherent benefit is that they can be used at the initial point of care. Moreover, they remain accurate even in the absence of baseline testing data.

Discussion

By many names, including Traumatic Brain Injury (TBI), Acute Traumatic Encephalopathy (ATE) or Sports Related Concussion (SRC), the medical community has long been aware of the negative cognitive and behavioral effects associated with forceful and repetitive impacts to the head. The literature synthesized in this review range from pathophysiological and mechanistic analysis of the injury itself to quantitative analysis and identification of unique diagnostic markers. However, they all address 1) the increased exposure risk that athletes in contact sports and military members experience and 2) the potential that improved identification of TBI could result in enhanced treatment strategies. These studies do this through their inclusion criteria and the conclusions they draw regarding trends in injury vulnerability, as well as their determinations regarding the utility and accuracy of existing diagnostic tools.

While TBI has traditionally been a symptomatic diagnosis, with mainly subjective criteria heavily reliant on self-reporting and the associated treatment plan utilizing those same assessments to determine degree of recovery, new research has identified objective clinical modalities that can identify someone as having experienced a TBI. Though symptomatic assessment remains the most practical modality for acute care, the identification of unique biomarkers that suggest persistence of BBB compromise or signal that the recovery phase has begun, provides an objective framework for clinical treatment. While some would argue that symptomatic monitoring is sufficient, the risk of subsequent insult prior to complete resolution of injury is too great to be approached solely subjectively.

The HEADSmart study avoids the subjective risk of symptom underreporting by introducing the use of biomarkers and neurocognitive assessments. However, when applied to predictive ability, it too suffers from reliance on subjective data. While the initial assessment is objective, the follow up requires subjects to self-report symptoms in an effort to validate the predictive ability of the biomarkers. Furthermore, there is a lack of subtlety in the "TBI" and "no TBI" classifications, resulting in a failure to address the severity of the injury and its correlation with certain levels of biomarker elevation or symptomatic presentation. Similarly, Vorn et al.'s study of proteomic profiling of plasma biomarkers relies heavily on the delineation

introduced by NCAA guidelines for a 14-day follow period in the event of SRC. The study thus lacks longitudinal data. Furthermore, comparison is between SRC with <14 day recovery period and ≥ 14 day recovery period, without the presence of a SRC-free control group. Though it does correlate that those in the recovery ≥ 14 days cohort had higher SCAT, BESS and BSI-18 symptom severity scores compared to the recovery <14 days cohort, the cohorts in and of themselves are flawed. Subjects are denoted as being of asymptomatic status according to their self-reported symptoms, which is a subjective assessment. Using that self-reporting process to determine cohorts creates an unreliable data set for statistical analysis. Rather, objective assessment scores should determine the cohorts, enabling prognostic and recovery markers to be explored based on evidence-backed cohorts rather than an arbitrary 14-day deadline determined by the NCAA for procedural purposes.

Albeit looking primarily at the pathophysiology of SRC, in their study of associated plasma biomarkers Vorn et al. also identified prognostic factors that could aid in clinical decision-making regarding preparedness for return to play. The presence of markers that are accessible *via* the limitedly invasive procedure of a blood draw could foreshadow an advancement in clinical decision making that would make SRC as definitive a diagnosis as a positive culture result. Eventually, biomarkers could be used to improve safety and long term outcomes by incorporating an objective, individual-performance-independent metric, into the return to sports decision.

The findings of the analysis of BBB permeability as a consequence of repetitive mild impacts further support the need for an objective assessment tool that would prevent athletes and servicemembers from returning to high-risk environments prior to complete recovery. However, it was not able to address the question raised during the study of what makes one rat or person, more resilient to TBI than another. This is an avenue for further exploration.

The study of time delta by Seifert et al. also recognizes the variability of individual resilience, yet similarly does not address the source of this inconsistency. They found that the same concussive impacts could cause a SRC in one athlete while leaving another asymptomatic. An evidence-supported hypothesis of an individualized concussion threshold dependent on genetics, medical history and biomechanical factors was proposed, but not explored and would be interesting to evaluate further in order to develop a method for quantifying biological risk.

Lastly, the conclusions from statistically analyzing multidimensional assessment models provides perhaps the clearest guide to clinical decision making. However, Garcia et al. fail to address new developments, such as the discovery of unique biomarkers that, albeit not practical for point of care diagnosis, could function as a valuable addition to clinical decision making as part of follow up care. The study also suffers from subjectivity bias in that there is significant variability in diagnoses given that they are being made by a diverse group of providers. Additionally, competitive athletes are more likely to underreport symptoms than almost any other group. Consequently, while multidimensional assessment models show SCAT to be a better assessment model comparatively, that should not invalidate objective evaluations, such as biomarkers, which were not included in this statistical analysis. By identifying those at high risk for repetitive trauma and ensuring a return to baseline prior to RTP clearance, there is the potential to improve long-term outcomes and prevent the development of chronic neurodegenerative symptoms.

The persistent flaw observed, to some degree, in every study is the use of subjective symptom assessment to determine diagnostic cohorts and drive recovery timeline. Using self-reported symptoms, either in the initial design or to validate a predictive algorithm, introduces bias because personal descriptions of individual experience is inherently biased. With knowledge about TBI constantly evolving, a longitudinal study featuring a cohort large enough to withstand attrition and encompassing the variability displayed in neurophysiology would be necessary to substantially evaluate the proposed predictive models.

Still, even if biological risk could be quantified, the question of what would be done to the prevent the injury remains. Is it the place of medical professionals to intercede and prevent an athlete from playing or keep a service member from combat because there is an increased risk? And if so, should the same exposure threshold apply to all or should individual resilience to TBI be considered?

Conclusion

Concussion is defined by care consortium as “a change in brain function following a force to the head, which may be accompanied by temporary loss of consciousness, but is identified in awake individuals with measures of neurologic and cognitive dysfunction.” However, in the time since that definition was established using evidence-based guidelines, new evidence has been discovered regarding the pathophysiology of head trauma. While unable to be applied on a sideline or battlefield at this point, such objective methods of testing could be inserted into existing clearance protocols to ensure full recovery prior to repeated exposure. Thus, the utility of biomarkers in preventing the long-term deficits that can result from repetitive head trauma is a promising development in the elimination of bias from TBI treatment, thereby protecting those with increased exposure risk.

Conflicts of Interest

No financial benefit was obtained as a result of this manuscript, nor is any benefit anticipated.

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