Concussion biomarkers

Timely and appropriate medical concussion treatment presents a difficult public health problem. Concussion diagnosis and treatment rely heavily on self-reporting, but more than half of concussions go unreported or are reported after a delay. If incomplete self-report increases exposure to harm, blood biomarkers may objectively indicate this neurobiological dysfunction.

The purpose of a study of D'Lauro et al. was to compare postconcussion biomarker levels between individuals with different previous concussion diagnosis statuses and care-seeking statuses. It was hypothesized that individuals with undiagnosed concussions and poorer care-seeking would show altered biomarker profiles.

Study design: Cohort study; Level of evidence, 3.

Blood samples were collected from 287 military academy cadets and collegiate athletes diagnosed with a concussion in the Advanced Research Core of the Concussion Assessment, Research, and Education Consortium. The authors extracted each participant's self-reported previous concussion diagnosis status (no history, all diagnosed, ≥1 undiagnosed) and whether they had delayed or immediate symptom onset, symptom reporting, and removal from activity after the incident concussion. The authors compared the following blood biomarkers associated with neural injury between previous concussion diagnosis status groups and care-seeking groups: glial fibrillary acidic protein, Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), neurofilament light chain (NF-L), and tau protein, captured at baseline, 24 to 48 hours, asymptomatic, and 7 days after unrestricted return to activity using tests of parallel profiles.

The undiagnosed previous concussion group (n = 21) had higher levels of NF-L at 24- to 48-hour and asymptomatic time points relative to all diagnosed (n = 72) or no previous concussion (n = 194) groups. For those with delayed removal from activity (n = 127), UCH-L1 was lower at 7 days after return to activity than that for athletes immediately removed from activity (n = 131). No other biomarker differences were observed.

Individuals with previous undiagnosed concussions or delayed removal from activity showed some different biomarker levels after concussion and after clinical recovery, despite a lack of baseline differences. This may indicate that poorer care-seeking can create neurobiological differences in the concussed brain [1)].

D'Lauro et al.'s study, published in the American Journal of Sports Medicine, investigates the relationship between blood biomarkers and concussion diagnosis and care-seeking behaviors. The study focuses on military academy cadets and collegiate athletes, aiming to identify potential neurobiological differences in individuals with undiagnosed concussions and those with delayed care-seeking.

One strength of the study lies in its use of a cohort design, providing valuable insights into the postconcussion biomarker levels in different groups. However, several limitations warrant critical consideration.

The reliance on self-reporting for concussion diagnosis and care-seeking behaviors introduces a significant source of bias. The authors acknowledge that more than half of concussions go unreported

or are reported after a delay, raising questions about the accuracy of the data. The study's level of evidence is categorized as 3, indicating a moderate level of evidence, which underscores the need for cautious interpretation of the findings.

The study focuses on four blood biomarkers associated with neural injury: glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain (NF-L), and tau protein. While the authors observed higher levels of NF-L in the undiagnosed previous concussion group at specific time points, the clinical significance and long-term implications of these differences remain unclear. Additionally, the lack of differences in other biomarkers raises questions about their relevance in the context of concussion diagnosis and care-seeking behaviors.

The study's sample size, particularly in the undiagnosed previous concussion group (n = 21), may limit the generalizability of the findings. Moreover, the inclusion of military academy cadets and collegiate athletes may not adequately represent the broader population, potentially limiting the external validity of the study.

The study suggests that individuals with undiagnosed concussions or delayed care-seeking may exhibit different biomarker levels after concussion and clinical recovery. However, the causal relationship between care-seeking behaviors and neurobiological differences remains unclear. It is essential to consider confounding factors, such as individual variability in response to concussions and other potential influencing variables, which the study does not thoroughly address.

In conclusion, while D'Lauro et al.'s study contributes to the growing body of literature on concussion diagnosis and treatment, its reliance on self-reporting, modest sample size, and potential for confounding factors highlight the need for further research to validate and extend these findings. Future studies should employ rigorous methodologies and diverse participant populations to enhance the generalizability and reliability of conclusions drawn from blood biomarkers in the context of concussion care-seeking behaviors.

The objective diagnosis of concussion remains challenging. Although some concussion symptoms may be apparent even to nonmedical observers, diagnosis and removal from play for evaluation depend on validated assessment tools and trained vigilant healthcare personnel. Over the past 2 decades, sideline concussion measures have undergone significant revision and augmentation to become more comprehensive batteries to detect a wide spectrum of symptomatology, eg, neurocognitive function, postconcussive symptoms, gait/balance, and saccadic eye movements. A review summarizes the current state-of-the-art concussion evaluation instruments, ranging from the Sports Concussion Assessment Tool (SCAT) and tools that may enhance concussion detection, to near-term blood-based biomarkers and emerging technology (eg, head impact sensors, vestibular-ocular/eye-tracking, and mobile applications).

● Concussion serum biomarkers: no moiety has been identified that can reliably diagnose concussion on serum or saliva testing. Neuron-specific enolase, S100, and cleaved tau protein have been studied for prognostication after mTBI and concussion. S100 has demonstrated only a 33.3% sensitivity for postconcussive symptoms and 93% sensitivity for an Extended Glasgow Outcome Scale < 5 at 1 month. Another study involving pediatric patients with mTBI showed no difference in levels of neuron-specific enolase or S100B in asymptomatic and symptomatic children. A prospective study found no significant correlation between cleaved tau protein and postconcussive syndrome in patients with mTBI [2)].

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D'Lauro C, Register-Mihalik JK, Meier TB, Kerr ZY, Knight K, Broglio SP, Leeds D, Lynall RC, Kroshus E, McCrea MA, McAllister TW, Schmidt JD; CARE Consortium Investigators:; Master C, McGinty G, Jackson JC, Cameron KL, Buckley T, Kaminski T, Mihalik JP. Optimizing Concussion Care Seeking: Connecting Care-Seeking Behaviors and Neurophysiological States Through Blood Biomarkers. Am J Sports Med. 2024 Feb 10:3635465231221782. doi: 10.1177/03635465231221782. Epub ahead of print. PMID: 38340366.
2)
Saigal R, Berger MS. The long-term effects of repeti- [35] tive mild head injuries in sports. Neurosurgery. 2014; 75 Suppl 4:S149–S155