Blood-Based Biomarkers for the Identification of Sports-Related Concussion

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KEYWORDS

• Sports-related concussion • Traumatic brain injury • Concussion • Biomarkers

KEY POINTS

- Sports-related concussion is common among athletes in the United States; however, current methods for sideline assessment are suboptimal because of their reliance on self-reported symptoms.
- Blood-based biomarkers have potential utility in sports-related concussion for diagnosis, prognostication, and identification of neurodegeneration.
- Several limitations exist in the current empirical literature that limit the current ability of biomarkers for use in this context; but with additional research and understanding of the neurobiological mechanisms, these limitations can be overcome.

INTRODUCTION

Sports-related concussions (SRCs) are common among athletes in the United States. The Centers for Disease Control and Prevention estimates that there are 1.6 to 3.8 million SRC per year[1] with the highest concussion rates found among contact sports, such as ice hockey, football, soccer, and basketball.[2] Most athletes who sustain an

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SRC recover within 7 to 10 days[3]; however, as many as 10% have prolonged postconcussion symptoms, such as headache and dizziness, which can persist much longer.[4–6]

There are multiple clinical definitions of concussion available; however, the 2 most widely used in the context of SRC are (1) the clinical definition of mild traumatic brain injury from the Centers for Disease Control and Prevention and (2) the definition of concussion from the "Consensus Statement on Concussion in Sport."[7] Both definitions include external force to the head that impairs neurologic functioning and the absence of structural damage to the brain on neuroimaging.

Sideline tools, such as the Standardized Assessment of Concussion[8] and the Sports Concussion Assessment Tool Versions 2 and 3,[3,7] are designed to assist coaches and certified athletic trainers to identify the neurophysiologic changes associated with concussion, such as loss of consciousness, amnesia, and confusion. Despite these standard tools, unrecognized or unreported concussions occur in more than half of high school football players.[9] This finding is evidenced by a recent study by Meehan and colleagues that found that one-third of athletes did not realize they had sustained a concussion and, thus, failed to report their injuries.[10] The reasons for this failure to diagnose SRC are multifactorial. Many of the current decision algorithms for diagnosis of concussion rely on patients' report of symptoms. However, this is often problematic, as assessments that rely on self-report assume the athletes' short-term memory is intact, although impairments in memory are one of the criteria for concussion diagnosis. Reliance on athletes' willingness to self-report also ignores the fact that, for many athlete populations, there is an incentive to hide or opt not to disclose symptoms because of a perceived or real fear of being removed from the team or engaging in sporting practices or contests. For many, the fear of being sidelined and restricted from play offsets the risk of not receiving treatment of the concussion injury.

Additionally, diagnosis of concussion in the emergency department is also problematic and faces similar challenges to sideline assessment. Studies have shown that health care providers failed to diagnose concussion in 56% to 89% of cases.[11–13] Accurate identification of concussion in the immediate postinjury period is critical, as failure to report and/or diagnose could result in long-lasting and catastrophic sequelae. Accurate and timely identification of SRC is important for (1) initiating a treatment protocol to limit the athlete's exposure to head hits and (2) for ensuring that the protocol is adhered to, to ensure full recovery. Full recovery for the athlete is essential to reducing excess concussion-related morbidity, such as second impact syndrome, which could be catastrophic.[7,14,15]

Because of the heavy reliance on self-report of symptoms in concussion diagnosis and the risks associated with missed concussion, there is a clear need to identify a time-sensitive and accurate method to identify SRC in the immediate postinjury period. Blood-based brain biomarkers (BBBMs) have been suggested as objective tools for the assessment of concussion diagnosis,[16–20] especially in this athlete population. BBBMs have the potential to aid not only in the diagnosis of concussion but also in the prognostication of symptom recovery and return to play (RTP) and identification of neurodegeneration.

In this document, the authors provide an overview of the empirical evidence related to the use of BBBMs in the athlete population for diagnosis of SRC, prognosis, and neurodegeneration from the injury. The authors also provide a summary of research challenges, gaps in the literature, and future directions for research.

NEUROBIOLOGY OF SERUM BIOMARKERS FOR TRAUMATIC BRAIN INJURY

The main structural correlate occurring after SRC is thought to be diffuse axonal injury (AI).[21] Biomechanical forces, such as head impacts, which occur during the course of