

Could concussion be monitored through urine samples?

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Concussion can be frustratingly hard to diagnose and track. The injury doesn't show up on routine brain scans, and there is no definitive diagnostic test. It's usually diagnosed based on symptoms, and, in athletes, comparison with baseline testing if it was done. But concussion symptoms are non-specific, unreliable, and easily influenced by

emotions.

"Athletes usually want to go back to their sport, so lots of times they say, 'I feel great, doc,' putting themselves at risk should they sustain a second brain injury," says William Meehan, MD, a physician in the Division of Sports Medicine at Boston Children's Hospital and director of The Micheli Center for Sports Injury Prevention. "But we've also had a lot of kids coming in worried, saying, 'I'm not doing so well in school and I play soccer. Could it be a concussion?' It would be great if a test could just tell us yes or no."

Rebekah Mannix, MD, MPH, in Boston Children's Division of Emergency Medicine, says 40 to 60 percent of concussions are missed in the acute setting, where more visible injuries tend to get the attention. "Concussion can be very subtle. But there are lots of reasons to want to diagnose concussion acutely—it can facilitate recovery, prevent kids from going back to sports too quickly, and avoid second-impact syndrome. We are always looking for objective markers of injury."

New research in the January 11 issue of *Neurology* could lead to just that: protein "biomarkers" in urine that could be used to diagnose concussion and monitor recovery.

A chance encounter

In 2015, David Howell, Ph.D., a postdoctoral fellow with Meehan, gave a talk at Boston Children's describing a study of concussion they were just beginning in collegiate athletes. Marsha Moses, Ph.D., director of the Vascular Biology Program at Boston Children's approached Howell afterward. "My lab works in the urinary biomarker space," she said. "We should talk."

Moses's work, going back more than 20 years, began as a way to detect

and monitor a variety of cancers. Several of her team's non-invasive urine tests are now in clinical trials. Over time, the team has also validated urinary biomarkers for chronic pelvic pain, benign prostatic hyperplasia, endometriosis, and more. Moses's renowned urine biorepository contains thousands of samples.

"In many illnesses, markers of physical and biological damage find their way into the bloodstream, and can often be found in the urine," Moses says. "Urine testing can be done early and often and is inexpensive compared to other types of tests."

A dialog quickly started up. "We had the study population, and Marsha's lab brought the scientific expertise of urine biomarker discovery and validation," says Howell, who is now at the University of Colorado.

Finding biomarkers of concussion

Until the pandemic, Moses and her team attended annual preseason evaluations at a local college. They consented the athletes and collected and froze their urine samples according to protocols established in the Moses Lab. Athletes who sustained a concussion (diagnosed by a sports medicine physician) provided a repeat urine sample within seven days, and again one, three, six, and 12 months after injury.

"As concussions occur, we wait for those samples to come in," says Cassandra Daisy of the Moses Lab, co-first author on the study with Howell and fellow Moses Lab member Speros Varinos. "Our population allows us to closely match athletes with and without concussion in terms of age and sex."

Eventually, the team gathered enough samples to compare the urine profiles of 95 athletes: 48 who sustained concussions and 47 controls. To measure proteins, they used mass spectroscopy in collaboration with

John Froehlich, Ph.D., and Richard Lee, MD, in Boston Children's Department of Urology, as well as enzyme-linked immunosorbent assays (ELISAs).

Of 71 proteins that differed significantly between the two groups, two stood out as the most predictive of concussion: IGF-1 and the IGF-binding protein 5 (IGFBP5), both found at significantly lower levels post-concussion. They appear to be involved in brain injury repair, so the body may retain them after concussion rather than excrete them. Used together and added to gait evaluations, the proteins distinguished between athletes with and without concussion with high reliability.

While the other proteins found were less predictive, many were quite interesting scientifically and could help in understanding the biological effects of concussion.

"We were surprised by what we didn't find," adds Daisy. "Known markers of severe brain injury didn't differ between the athletes with concussion and controls. Concussion appears to be very different."

Testing concussion biomarkers in other groups

With these biomarkers for concussion in hand, the team now aims to validate its proof-of-principle study through clinical trials in different populations, such as a broader college athlete population, adolescents playing sports, and people with non-sport-related concussions. Eventually, the goal is to develop a test that could be available at the point of care and even at the time of injury.

"As with COVID-19, if you have symptoms but aren't sure of the cause, it would be ideal to have a test to diagnose [concussion](#) or rule it out," says Howell.

More information: Cassandra C. Daisy et al, Proteomic Discovery of Noninvasive Biomarkers Associated With Sport-Related Concussions, *Neurology* (2021). [DOI: 10.1212/WNL.00000000000013001](https://doi.org/10.1212/WNL.00000000000013001)

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