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Lubricating the knee cartilage after ACL injury may prevent osteoarthritis

PROVIDENCE, RI – An injury to the anterior cruciate ligament (ACL) is fairly common, especially among young athletes. While it can often be corrected through surgery, the injury can lead to increased risk of developing degenerative joint diseases, including osteoarthritis (OA). The problem is that fluid in the knee joint, which lubricates the cartilage, is impacted by the trauma of the injury and begins to deteriorate. A new study from Rhode Island Hospital researchers identifies options for restoring that lubrication to potentially prevent development of OA. The study is published in the August 2010 edition of the journal *Arthritis & Rheumatism* and is now available online ahead of print.

The study was led by Gregory Jay, MD, PhD, an emergency medicine physician and researcher at Rhode Island Hospital. Jay says, "We know that acute ACL injury is a significant risk factor for the development of post-traumatic osteoarthritis. We also know why that occurs, due to the degeneration of the fluids in the joint and cartilage and joint instability, among other things. Our goal for this study was to determine an effective way to counter that process to prevent the development of OA."

The most movable joints in the body, known as synovial joints, contain synovial fluid (SF). This fluid acts as a lubricant to reduce friction between cartilage in the joint during movement. Following a traumatic injury to the ACL, SF concentration of the natural lubricant, lubricin, in the injured joints is significantly lower in those joints than in the healthy, uninjured joint.

The goal was to identify biologic methods to address the loss of lubricin. In their study, they used animal models with torn ACLs to test three types of fluids that could be injected into the joints and could serve as a substitute for the lost SF. The first was human synoviocyte lubricin that was created in a culture and then purified to be injected into the injured knees. The second is recombinant protein, with a change in the genetic make-up of the cell so that it makes a molecule of interest. The reasoning behind using a recombinant protein is that if it is commercialized, that is likely how it will be manufactured. The third was lubricin from human SF that would otherwise be discarded. The human SF is then purified before

injection, and because it is more closely aligned with the natural lubricin, it represents a positive control in the study.

Through their study, the researchers report three key findings. Jay, who is also a professor of emergency medicine and engineering at The Warren Alpert Medical School of Brown University says, "First and foremost, we found that you can limit cartilage deterioration. This is evident by using a well-accepted OA biomarker which shows that the breakdown of cartilage collagen type 2 and recovered in the urine has been muted by treating the knee joint with lubricin." The human synoviocyte lubricin was the most effective form in this experiment, however, the recombinant form also had a good degree of success.

Second, the study results indicate that when lubricin is placed back into the traumatized joint, it encourages the joint to make its own lubricin. Jay explains, "We found that you are limiting deterioration of the joint endogenously by the greater secretion of the lubricin molecule. Basically, by placing the lubricin there, it encouraged the joint's normal activity to produce this molecule."

Jay, who is also a physician with University Emergency Medicine Foundation in Providence, stresses that this study is important for another reason. "This is a huge advance over the existing technology of viscosupplementation injections. The concept was good, but the chemistry isn't there to support it." Jay continues, "When viscosupplements were approved as devices in the 90s, it was thought then that hyaluronic acid used in this treatment was tied to joint lubrication because it was viscous. We now know that joint lubrication has little to do with viscosity. We are inventing a new type of joint lubrication strategy: Tribosupplementation, taken from the Greek, meaning to wear or to rub" "

Jay notes, "Viscosupplementation is a $500 million per year device market that just doesn't work particularly well. Past studies by us and others indicate this. We now need a paradigm shift in how we are thinking about preventing and treating arthritic diseases."

Jay and his colleagues believe the study findings represent that paradigm shift. Jay says, "We found that lubricin may prevent the fundamental process that can lead to OA following an ACL injury. It is a promising biologic candidate since it is a replacement for a normally occurring glycoprotein. This is very germane to the health care bill, which supports the creation of new therapeutic biologics." Biologics are important and their development is encouraged because they are very specific and have low toxicity profiles, meaning they are better for patients in terms of better results with fewer complications.

Jay concludes that this and related papers are key to future treatment of joint trauma. "In the peri-injury period following joint trauma, joint surfaces are vulnerable to enhanced wear. This study is pointing us in the right direction, and has shown that this can potentially be mitigated by simply reintroducing the joint's natural lubricant." He continues, "We are confident that further studies will perfect the technology and this will be the way that joints will be treated in the future to prevent OA."

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The research was supported by grants from the National Institutes of Health and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Other researchers working with Jay include Braden C. Fleming, Ling X. Zhang and Erin Teeple of Rhode Island Hospital and Brown University; Kimberly A. Waller of Brown University; Bryn A Watkins, Karen A. McHugh, and Scott C. Anderson of Biomodels and Khaled A. Elsaid of the Massachusetts College of Pharmacy and Health Sciences. (Citation: Jay GD, Fleming BC, Watkins BA, McHugh KA, Anderson SC, Zhang LX, et al. Prevention of cartilage degeneration and restoration of chondroprotection by lubricin tribosupplementation in the rat following anterior cruciate ligament transection. Arthritis Rheum 2010;62:2382-91.)

About Rhode Island Hospital

Founded in 1863, Rhode Island Hospital (www.rhodeislandhospital.org) in Providence, RI, is a private, not-for-profit hospital, the largest teaching hospital of The Warren Alpert Medical School of Brown University and a founding member of the Lifespan health system. A major trauma center for southeastern New England, the hospital is dedicated to being on the cutting edge of medicine and research. Rhode Island Hospital receives nearly $50 million each year in external research funding. It is also home to Hasbro Children's Hospital, the state's only facility dedicated to pediatric care.
