Male, female knee cartilage disparities may explain differences in rates of degeneration

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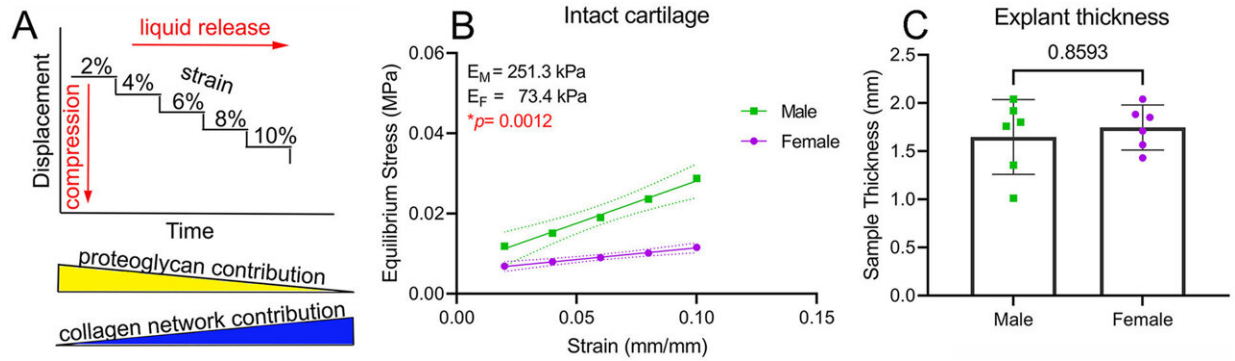

Dimorphism in cartilage network mechanics. (A) Schematics of the stress relaxation test used. The expected relative contribution of proteoglycans and collagen networks to equilibrium modulus are indicated at the bottom of the graph. (B) Equilibrium modulus calculated from the linear portion of the stress-strain curve in intact cartilage. (C) Sample thickness of intact cartilage samples. Data in B and C are presented as mean ± 95% CI (dotted lines in B); n = 6♂ and 6♀, with each measured in duplicate. CI = confidence interval. Credit: *CARTILAGE* (2022). DOI: 10.1177/19476035221121792

Researchers have long known there are sex disparities when it comes to the prevalence and severity of knee osteoarthritis, a disease that causes cartilage degeneration. Now, investigations underway at UT Southwestern Medical Center point to biological differences in the knee cartilage of male and female animals that could explain substantial variances in rates of osteoarthritis between the sexes and may eventually

lead to tailored treatments that take these into account.

"If we really want to improve women's health in orthopedics, we have to understand how men and women are different at the tissue, cellular, and molecular level," said Paula Hernandez, Ph.D., Instructor of Orthopaedic Surgery at UTSW, and Biomedical Engineering at UTSW, who leads research on structural, cellular, and mechanobiological aspects of sexual dimorphism in cartilage. "This is a start toward identifying those differences."

Articular cartilage acts as a cushion in our joints, allowing for frictionless movement, and its degeneration can be painful and debilitating. Several tissues within the knee joint including cartilage, meniscus, and ligaments work in balance to provide mechanical stability to the knee. Women are more susceptible than men to injuries of the anterior cruciate ligament (ACL), a key to knee stability, and that damage can result in a mechanical imbalance exposing cartilage to injurious friction and excessive mechanical load, triggering degeneration .

Because many women experience joint problems after menopause, Dr. Hernandez explained, the prevailing hypothesis has been that hormonal changes accompanying this life stage were responsible for differences with men. However, she and her colleagues wondered whether the factors that could contribute to joint issues were present far earlier.

To answer this question, Dr. Hernandez and her team worked with cartilage from the knees of cows between 24 and 30 months old—equivalent to humans 18 to 20 years old. This material is very similar to human cartilage but far easier to acquire from animal models than human patients, she said.

The study, published in *Cartilage*, found that knee cartilage isolated from

male and female animals differed significantly in mechanical properties, microstructure, and gene expression long before hormonal changes from menopause.

Mechanical tests revealed that bovine cartilage from the males was more than three times stiffer than that from females. When the researchers examined the protein content of this cartilage, they found significant differences in the content of specific protein types in tissue from the male and female animals. Treating individual chondrocytes—the cells that produce cartilage—with an inflammatory chemical changed the activity in different sets of genes between the sexes.

Dr. Hernandez said these findings show striking differences in cartilage between the males and females relatively early in life—long before the end of these animals' reproductive period. Her team is continuing to investigate when these differences first appear and whether they're tied to chromosomal sex, sex hormones, or another cause.

"By better understanding the root cause of sex differences and embracing them," Dr. Hernandez said, "we can get closer to closing the gap in knee osteoarthritis between the sexes."

More information: Paula A. Hernandez et al, Sexual Dimorphism in the Extracellular and Pericellular Matrix of Articular Cartilage, *Cartilage* (2022). DOI: 10.1177/19476035221121792

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