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The tribology of cartilage: mechanisms, experimental techniques, and relevance to translational tissue engineering

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Abstract

Diarthrodial joints, found at the ends of long bones, function to dissipate load and allow for effortless articulation. Essential to these functions are cartilages, soft hydrated tissues such as hyaline articular cartilage and the knee meniscus, as well as lubricating synovial fluid. Maintaining adequate lubrication protects cartilages from wear, but a decrease in this function leads to tissue degeneration and pathologies such as osteoarthritis. To study cartilage physiology, articular cartilage researchers have employed tribology, the study of lubrication and wear between two opposing surfaces, to characterize both native and engineered tissues. The biochemical components of synovial fluid allow it to function as an effective lubricant that exhibits shear-thinning behavior. Although tribological properties are recognized to be essential to native tissue function and a critical characteristic for translational tissue engineering, tribology is vastly understudied when compared to other mechanical properties such as compressive moduli. Further, tribometer configurations and testing modalities vary greatly across laboratories. This review aims to define commonly examined tribological characteristics and discuss the structure-function relationships of biochemical constituents known to contribute to tribological properties in native tissue, address the variations in experimental set-ups by suggesting a move toward standard testing practices, and describe how tissue-engineered cartilages may be augmented to improve their tribological properties.

Keywords

tribology; diarthrodial joint; articular cartilage; meniscus; synovial fluid; tissue engineering

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Introduction

Diarthrodial joints, such as the knee, contain hyaline articular cartilage, fibrocartilage, and intra-articular space filled with synovial fluid. Hyaline articular cartilage is a highly hydrated, anisotropic tissue composed primarily of collagen II, proteoglycans, and chondrocytes that covers the ends of long bones and acts as a load-bearing, lubricated surface during joint articulation.(Athanasίου et al., 2017) Fibrocartilage structures, such as the meniscus in the knee, confine motion, dissipate loads, and contribute to essentially frictionless articulation of diarthrodial joints as well. Synovial fluid is confined to the joint space by the articular capsule and contains macromolecular components, such as superficial zone protein (SZP) and hyaluronan, which are essential to joint lubrication.(Jay and Waller, 2014; Noyori et al., 1998) This review will focus on the articular surfaces of hyaline articular cartilage and the knee meniscus, as well as synovial fluid, since they are the components responsible for maintaining low-friction motion and lubrication, or tribological functions, in diarthrodial joints.

Tribology is the study of the interactions between two surfaces moving relative to one another. While it traditionally refers to the study of non-biological materials, tribological principles have been extended to understand the loading environment of diarthrodial joints. The quantitative properties when studying the tribology of diarthrodial joints are surface roughness, R_a , and coefficient of friction, μ . This review will utilize both of these properties for evaluation of tribological properties of the native and engineered tissues described in subsequent sections. A crucial characteristic of native hyaline articular cartilage is its ability to exhibit minimal friction at joint-gliding speeds between 0–0.03m/s when subjected to loads that are five times bodyweight.(Bergmann et al., 1993; Morrell et al., 2005) The replication of tribological properties is crucial to the translation of tissue-engineered articular cartilages, yet they remain under-characterized in tissue-engineered constructs. For instance, a PubMed search for “articular cartilage lubrication” yielded 422 results, but a search for “articular cartilage mechanical properties” produced 1,789 references. Building on some of the tissue-engineering strategies described in this review to improve the tribological properties of engineered constructs could decrease this discrepancy.

It is predicted that by the year 2050 osteoarthritis, an articular cartilage degeneration disease, will affect at least 130 million people world-wide.(Maiese, 2016) Articular cartilage degeneration causes pain and inflammation of the joint, loss in mechanical function, as well as loss in tribological function. As health care technologies expand and life expectancy in the United States consequently increases, incidences of articular cartilage degeneration will also increase, necessitating viable treatment options such as implantable tissue-engineered articular cartilage constructs with adequate mechanical and tribological properties.

In this review, the components, such as SZP and hyaluronan, and mechanisms, such as shear-thinning of synovial fluid, known to contribute to the tribological properties of articular cartilages will be described. The pathologies that compromise articular cartilage tribological function will also be discussed. Specifically, this review will delve into how surface roughness, coefficient of friction, and lubrication regimes affect and are affected by the state of biochemical components known to regulate tribological function. Tribological

properties will be compared quantitatively by looking at the spread of the coefficient of friction obtained across laboratories using a variety of tribometer modalities. Although there is a consensus toward testing articular cartilages under boundary lubrication regimes, variations exist from laboratory to laboratory in terms of tribometer configurations, testing substrates, and lubricants. A recommendation will be made toward reconciling and standardizing tribological measurements for articular cartilages. Therapeutic targeting of tribological properties will be presented and discussed, including the current state of recapitulating tribological properties in tissue-engineered articular cartilages for translation. Finally, the areas of articular cartilage tribology that remain understudied will be presented.

Commonly examined tribological characteristics in cartilage

The two quantitative tribological characteristics measured in both native and engineered articular cartilage are surface roughness and coefficient of friction. In this section, surface roughness and coefficient of friction are defined, and the values of native articular cartilage are presented. Finally, the coefficient of friction and surface roughness of synthetic materials are juxtaposed to native cartilage tribological properties for added context and perspective.

Surface roughness

A common measure of surface roughness, R_a , quantifies asperities on the articulating surface. Surface roughness is derived by measuring the average height deviation from the surface midline and is typically reported in nanometers.(Zappone et al., 2008) Surface roughness ranges from 1–150 nm in native hyaline articular cartilage across the body. In comparison, the femoral head components of total hip replacements typically range from 40–200 nm in surface roughness.(Ghosh and Abanteriba, 2016; Ghosh et al., 2013; Moa-Anderson BJ, 2003)

Coefficient of friction

Coefficient of friction, μ , refers to the ratio of the horizontal force needed to move two surfaces across each other relative to the normal force. Coefficient of friction is the tribological property most studied in the field of articular cartilage. In both native and experimental settings, coefficient of friction is dependent on the articular surface roughness, normal load, lubrication mode, as well as experimental conditions such as testing modality. Coefficient of friction may be determined under static or kinetic conditions. Furthermore, the initial and equilibrium coefficient of friction can also be measured. The coefficients of friction that will be examined in this review were obtained under kinetic, equilibrium conditions in the boundary lubrication regime. The coefficient of friction of native articular cartilage has been reported to range broadly from 0.001–0.45 (Table 1).(Athanasίου et al., 2017; McCutchen, 1962; Middendorf et al., 2017). For comparison, typical new and cleaned rolling bearings offer a coefficient of friction of 0.005, indicating that articular cartilage can be more frictionless than a man-made bearing under certain conditions.(Woydt and Wäsche, 2010)

Tribological structure-function relationships in diarthrodial joints

In this section, the cartilage components that are essential for tribological function are identified. The capacity of lubricin and hyaluronan to modify the tribological characteristics of a diarthrodial joint is described. The importance of the interaction between lubricin and hyaluronan in the synovial fluid is also described and further discussed in the context of different lubrication modes. Lubrication modes, including boundary, mixed, elastohydrodynamic, and hydrodynamic, are defined, and the loading conditions that yield these lubrication modes are also established.

Cartilage components essential for tribological function

Among the components of diarthrodial joints, synovial fluid and the articular cartilage surface, or lamina splendens, play particularly important roles in cartilage lubrication. (Athanasίου et al., 2017) Two key synovial fluid constituents are hyaluronan and SZP. (Majd et al., 2014). Hyaluronan, among other roles, gives rise to the shear-thinning properties of synovial fluid, critical to fluid film lubrication in articulating joints. (Tamer, 2013) Matrix molecules present at the articular cartilage surface, primarily collagen II, can form molecular associations with SZP and hyaluronan in synovial fluid. (Flowers et al., 2017; Majd et al., 2014) These complexes at the cartilage surface create a “sacrificial layer” vital in mediating boundary lubrication. (Chan et al., 2012) Due to their vital functions in mediating cartilage lubrication, SZP and hyaluronan are discussed in more detail below.

Lubricin/SZP/proteoglycan 4: Lubricin, SZP, and proteoglycan 4 (PRG4) are terms often used interchangeably throughout the literature to describe one of the critical lubricants in diarthrodial joints. While each is a product of the *PRG4* gene, they are distinct macromolecules of varying sizes (SZP: 345 kDa, lubricin: 227 kDa, PRG4: 460 kDa). (Peng et al., 2015) However, because it is difficult to distinguish unique functions among them, this review will refer to the products of the *PRG4* gene collectively as SZP. This is a mucinous glycoprotein secreted into synovial fluid by superficial zone chondrocytes and synoviocytes, shown to mitigate superficial zone cartilage damage and chondrocyte death. (Jay and Waller, 2014)

The globular N- and C- termini of SZP can interact with a variety of molecules at the cartilage surface, such as collagen II, fibronectin, and cartilage oligomeric protein to form a lubricating boundary layer. (Flowers et al., 2017; Jay and Waller, 2014) SZP has also demonstrated strong adsorption to denatured, amorphous, and fibrillar collagen II, suggesting its adsorption is not dependent on the conformation of collagen. (Chang et al., 2014) Meniscus surfaces can also benefit from this lubricating layer, because SZP localization at its surface has been observed. (Warnecke et al., 2017) In general, SZP has been shown to reduce coefficients of friction across a variety of tissues and materials. (Chang et al., 2014; Jay and Waller, 2014; Peng et al., 2015) Its function can be further enhanced in the presence of hyaluronan, with which it can interact to form complexes. (Greene et al., 2011)

Hyaluronan: The non-sulfated glycosaminoglycan (GAG) hyaluronan is a large polysaccharide (2000 kDa in diarthrodial joints) that is found both floating freely in synovial

fluid and as part of the extracellular matrix of articular cartilage.(Cowman et al., 2015) GAGs are thought to be responsible for interstitial fluid pressurization in articular cartilage, and the depletion of GAGs, in particular hyaluronan, has adverse effects on its frictional and lubricating properties. (Comper and Laurent, 1978; Higaki et al., 1998) For example, gradually removing hyaluronan from a lubricating solution was shown to increase the coefficient of friction of the native articular cartilage surfaces being examined.(Higaki et al., 1998) Hyaluronan in a matrix is known to act as a viscoelastic material, and, because of its large size, hyaluronan induces steric hindrance that attenuates fluid flow within a solution. (Comper and Laurent, 1978; Šimkovic et al., 2000; Tamer, 2013) Since these properties of hyaluronan contribute to joint tribology, several hyaluronan-based clinical products have been developed to mitigate the symptoms of osteoarthritis.(Sun et al., 2017; Tamer, 2013)

In experimental laboratory settings, hyaluronan has been studied as a joint lubricating agent using cartilage-cartilage, cartilage-steel, and cartilage-glass interactions.(Bell et al., 2006; Higaki et al., 1998; Murakami et al., 1998) Furthermore, hyaluronan alone, and its complexing with SZP, contribute greatly to the shear-thinning behavior of synovial fluid, suggesting that a healthy joint necessitates both hyaluronan and SZP for tribological function.(Greene et al., 2011) Therefore, when studying and characterizing the tribology of diarthrodial joint tissues, both hyaluronan and SZP should be present in the testing solution if one is to expect coefficients of friction approximating *in vivo* values.

Regulation of lubrication modes in diarthrodial joints

The shear-thinning properties of synovial fluid allow it to act as a viscous fluid at low shear rates or sliding speeds.(Ambrosio et al., 1999; Hyun et al., 2002) The loading and shear rates that affect the viscosity of synovial fluid also influence the lubrication mode (boundary or fluid-film) and tribological properties of articulating joints. Because of the inherent porosity of articular cartilage, it is theorized that the articular cartilage “weeps” interstitial fluid into the intra-articular space when pressurized. When in fluid-film lubrication, pressure on the fluid in the intra-articular space drives fluid into the tissue, theoretically “boosting” its mechanical properties.(Lewis and McCutchen, 1959; McCutchen, 1959; Walker et al., 1968) Stribeck curves, such as the one shown in Figure 1, are used to plot the dependence of the coefficient of friction on sliding speed, applied normal load, and viscosity of the fluid between the sliding surfaces, and illustrate how these parameters determine the mode (i.e., boundary or fluid-film) and regime of lubrication. These lubrication regimes are boundary (Figure 1A), mixed (Figure 1B), elastohydrodynamic (Figure 1C), and hydrodynamic lubrication (Figure 1D), which will be discussed in greater detail below.

Boundary lubrication plays a crucial role in articular cartilage tribology and mediates frictional properties of articular cartilages if the joint is functioning under high loads, low sliding speeds, or high fluid viscosity.(Chan et al., 2010; Gleghorn and Bonassar, 2008) *In vivo* and cadaveric studies have shown that under physiological loads, the pressure distribution and lubrication regimes across the articular cartilage surface are not uniform, and, in areas of high load, articular cartilage surfaces experience boundary lubrication. (McCutchen, 1959) Most studies examining the tribological properties of articular cartilage surfaces conduct measurements under a boundary lubrication regime because of its

translational relevance, since this regime interrogates sample properties rather than lubricant properties (Table 1 and Table 2). In the boundary lubrication regime, articular cartilage surfaces are separated by only one or two molecules, known as a sacrificial layer.(Chan et al., 2012) The primary molecules responsible for forming the layer of separation are hyaluronan and SZP, which shelter the articular cartilage surface from high friction.(Neu et al., 2008) Other molecules involved in forming the sacrificial layer are aggrecans and surface-activated phospholipids.(Jahn et al., 2016) This sacrificial layer of molecules lining articular cartilage in boundary lubrication mode is replenished at an equal or higher rate than it is depleted, which maintains a low coefficient of friction on the articular cartilage surface. Studies have shown that in healthy articular cartilage, the boundary lubrication layer would be replenished at least 10 times faster than the development of wear caused by an increase in friction coefficient.(Chan et al., 2012)

Fluid-film lubrication occurs at high articulation speeds or low loads. Fluid-film lubrication can be either elastohydrodynamic or hydrodynamic depending on these loading conditions, but is classified as fluid film lubrication if the interacting articular cartilage surfaces are fully separated by a fluid-film distance larger than the surface roughness of the tissue.(McNary et al., 2012) If the articular cartilage surface is deformed by the fluid-film, then lubrication is considered to be in the elastohydrodynamic regime. Under the elastohydrodynamic regime, joint physiological loads are initially borne by the synovial fluid; the corresponding fluid pressure is then transferred onto the articulating surfaces. In fluid-film mode, the complex formed by SZP and hyaluronan is disassembled because of their weak physical interaction. (Zappone et al., 2008) This allows SZP to float freely in the synovial fluid and disperse evenly throughout the intra-articular space.(Greene et al., 2011)

Pathologies affecting diarthrodial joint tribology

Conditions that can induce cartilage degeneration and, consequently, a reduction in tribological properties, include congenital disorders, wear and tear, traumatic injury, and inflammation. One congenital disease with particular relevance to cartilage lubrication is camptodactyly-arthropathy-coxa vara-pericarditis (CACP) syndrome, caused by a mutation in the *PRG4* gene.(Jay and Waller, 2014) Inherited in an autosomal recessive fashion, affected patients exhibit non-inflammatory, juvenile-onset joint failure, suggesting SZP is necessary for joint health and function.(Marcelino et al., 1999) The ability of SZP to rescue function in tissues affected by CACP has been tested *in vitro* using bovine articular cartilage. (Waller et al., 2013) These explants demonstrated a boundary mode friction coefficient of 0.04 when lubricated with synovial fluid taken from patients with CACP (i.e., lacking functional SZP). When SZP was added to the CACP synovial fluid, however, the coefficient of friction dropped to 0.005. Thus, functional SZP appears to be a critical regulator of cartilage lubrication.

In addition to genetic conditions, general wear and tear of the articular surface can lead to local collagen depletion, one of the first stages of osteoarthritis.(Grenier et al., 2014) Superficial collagen loss likely depletes the cartilage surface of key boundary lubrication components, such as SZP, hyaluronan, and binding domains, and can increase surface roughness, potentially furthering the progression of osteoarthritis.(Coles et al., 2010; Jay et

al., 2007) Differences in gross morphology, biochemical content, and mechanical properties between healthy and diseased cartilages are depicted in Figure 2. Healthy human femoral head articular cartilage has demonstrated a boundary mode coefficient of friction of 0.119, whereas early osteoarthritic tissue and advanced osteoarthritic tissue had friction coefficients of 0.151 and 0.409, respectively.(Park et al., 2014) Values were determined using atomic force microscopy (AFM), thus surface roughness was simultaneously measured. The increase in friction coefficients with osteoarthritis progression correlated with higher tissue surface roughness, as it was determined healthy, early osteoarthritic, and advanced osteoarthritic tissue each had a surface roughness of 104, 382, and 537 nm, respectively. These findings indicate osteoarthritis progression is closely related to deteriorating cartilage lubrication.

Traumatic injury often induces post-traumatic osteoarthritis, a condition that can inhibit the lubrication of articular cartilages. For example, in an equine injury model, synovial fluid hyaluronan concentration and molecular weight decreased following the injury, which impacted the fluid's lubrication abilities. The boundary mode friction coefficient of bovine articular cartilage tested in healthy equine synovial fluid was 0.026, whereas it was 0.036 when tested with synovial fluid from injured horses.(Antonacci et al., 2012)

Inflammatory pathways can also be activated by traumatic injury and osteoarthritis, leading to the upregulation of inflammatory cytokines such as interleukin-1 β (IL-1 β), known to adversely affect lubrication of articular cartilage.(Gleghorn et al., 2009) In an *in vitro* study, 48-hour IL-1 β treatment of bovine cartilage explants increased the boundary mode equilibrium coefficient of friction from 0.26 to 0.36. It has also been shown that an important regulator of cartilage lubrication and superficial zone maintenance is epidermal growth factor receptor (EGFR). In an animal study, EGFR-deficient mice developed early cartilage degeneration and demonstrated little to no hyaluronan and SZP localization at the cartilage surface.(Jia et al., 2016) In bovine articular cartilage explants, transforming growth factor alpha (TGF- α), known to activate EGFR-signaling, led to nearly a six-fold increase in *PRG4* mRNA and a 28% reduction in the explant friction coefficient. Thus, if EGFR-signaling is disrupted in articular cartilage, for instance through upregulation of IL-1 β , key lubrication components, tissue tribological properties, and overall tissue health can be damaged.(Jia et al., 2016; Sanchez-Guerrero et al., 2012) In general, regardless of the mechanism of depletion, a lack of boundary lubricant will increase frictional forces in the superficial zone of articular cartilage, potentially leading to dysregulated chondrocyte metabolism, apoptosis, and degeneration.(Waller et al., 2013)

Methods for quantifying tribological properties

In this section, methods for quantifying tribological properties are listed and discussed. The most commonly used tribometer configurations, pin-on-disc, pin-on-plate, and rolling-ball-on-disc, for articular cartilage are described and compared. The use of atomic force microscopy to quantify surface roughness is also included. Because different testing configurations can lead to disparities in coefficient of friction and surface roughness values, suggestions for standardized practices are also presented.

Tribometers

A tribometer quantifies tribological properties, such as coefficient of friction. There are many different tribometer configurations across engineering, but the most popular in articular cartilage research are pin-on-disc, pin-on-plate, and rolling-ball-on-disc (Figure 3). Regardless of the configuration, all tribometers aim to measure the properties of two materials rubbing against each other and the effectiveness of lubricants between them. Usually, articular cartilages are tested against a substrate of either stainless steel or glass, with lubricants ranging from phosphate buffered saline (PBS) solution to fetal bovine serum. To showcase the multitude of ways tribological properties are studied, Table 1 and Table 2 compare recent tribology studies on hyaline articular cartilage, as well as the knee meniscus, by describing sample types, tribometer configurations, substrates, and lubricants. In particular, Table 1 demonstrates how these experimental methodological variations yield large discrepancies in the coefficient of friction of native articular cartilages. For example, quantifying coefficient of friction by using cartilage-on-cartilage will yield lower values compared to using glass-on-cartilage.(Warnecke et al. 2017) Furthermore, the testing solution also has an effect on coefficient of friction, such as BSF yielding lower values compared to PBS.(Schmidt et al. 2007) It is emerging that having a standard practice of quantifying coefficient of friction of native and engineered articular cartilage would be useful in facilitating comparisons between laboratories. For instance, this standard method could involve a pin-on-plate or pin-on-disc tribometer configuration with the tissue submerged in PBS under boundary lubrication.

Pin-on-disc/plate: The pin-on-disc and pin-on-plate tribometer configurations are the most popular amongst articular cartilage research groups. Usually, they contain an acrylic pin to which articular cartilage samples may be glued and then placed in contact with a substrate (Figure 3A and Figure 3B).(Bonnievie et al., 2014; Kanca et al., 2018a; Shi et al., 2011) The disc or plate substrate, generally made of glass or stainless steel, is completely submerged in a lubricating fluid, such as PBS, for testing. Adjustable weights are used to apply a known normal force on the articulating surfaces. A strain gauge, or other force sensor types, is used to measure the friction force of the sample as the disc or plate rubs against it. Boundary lubrication mode should be the lubrication modality used for this tribometer configuration to ensure that the properties that are observed reflect the properties of the sample against the substrate. If identification of the lubrication properties of a solution is desired, both boundary and fluid-film lubrication studies should be performed to fully characterize the lubricant.

Rolling-ball-on-disc: Tribometers may also take the form of a rolling-ball-on-disc (Figure 3C). In this configuration, both the ball and the disc can be driven independently allowing for a variety of kinematic conditions.(Neas et al., 2018) This configuration is generally used to test the interaction of substrates used in total knee replacements and is useful for testing the wear characteristics of plastic inserts and metal components in synthetic joint replacements over time. Although useful for certain applications, the rolling-ball-on-disc tribometer does not feasibly allow the testing of a small articular cartilage tissue sample. Ball-on-disc tribometers, although rarely used, also exist and differ from rolling-

ball-on-disc tribometers in that the ball is used to translate against a sample without rolling. (Blum and Ovaert, 2013; Grad et al., 2012)

Atomic force microscopy

AFM is capable of surface imaging and force measurements at the nanoscale, making this approach valuable for measuring tribological properties such as surface roughness and “microscale” coefficient of friction. (Park et al., 2004) Through the use of AFM, it has been found that the surface roughness, R_a , of immature bovine articular cartilage is around 72 nm. (Moa-Anderson BJ, 2003) AFM is particularly useful for testing tribological properties occurring under boundary lubrication because of its ability to operate at single asperity, high pressure contact. (Chan et al., 2010) However, studies have shown that AFM tip size and scan size affect surface roughness measurements. (Sedin and Rowlen, 2001) Therefore, when presenting AFM measurements for surface roughness, it is also important to report the tip size and scan size, as well as a native tissue measurement with the same tip size and scan size, for comparison.

Toward engineering native tribological properties

Because adequate lubrication is vital for diarthrodial joint health and function, various strategies to engineer biomimetic tribological properties for both native tissue and engineered constructs have been explored. Approaches include the development of biolubricants to alter both fluid-film and boundary lubrication, low-friction scaffolds, as well as bioactive factors and mechanical stimulation regimens that promote endogenous lubrication mechanisms.

Biolubricants

Biolubricants can augment boundary lubrication properties by binding to articular cartilage to replace components often depleted in damaged or degenerated articular cartilage, such as GAGs. For example, hyaluronan-binding peptides were attached to cartilage via heterobifunctional polyethylene glycol (PEG) chains to recruit hyaluronan from solution to the cartilage surface. (Singh et al., 2014) This strategy significantly decreased coefficients of friction in both healthy and osteoarthritic cartilage explants by ~50% relative to control conditions (i.e., PBS as the lubricant) and could be retained in the rat joint for at least 72 hours, much longer than hyaluronan alone. Importantly, in osteoarthritic cartilage explants, high concentration of hyaluronan in the testing solution did not reduce friction coefficients relative to the hyaluronan-binding system applied to the same tissue type, indicating that even low levels of hyaluronan, when bound to a surface, can improve lubrication properties. (Singh et al., 2014) Samples in this study were tested in a pin-on-disc (in this case, tissue-on-tissue) configuration within the boundary lubrication regime.

There are already clinically available hyaluronan-based biolubricants, or viscosupplements, such as Artz®, Healon®, Hyalgan®, Opegan®, Opelead®, Orthovisc®, and Synvisc-One®. (Sun et al., 2017; Tamer, 2013) While some patients experience a transient improvement in their osteoarthritis symptoms after treatment, evidence is lacking to demonstrate the clinical efficacy and disease-modifying ability of these injections. (Henrotin et al., 2018) In a similar

context, modified, recombinant SZP as an intra-articular injection has been investigated preclinically in a rat osteoarthritis model.(Flannery et al., 2009) 1 week following osteoarthritis induction, SZP injections were administered for 4 weeks before animal sacrifice, significantly improving total joint scores and reducing cartilage degeneration. Like hyaluronan viscosupplementation, however, the long-term clinical efficacy of SZP injections remains to be elucidated.

In another study, a poly(glutamic acid) backbone (PGA) was modified with poly(2-methyl-2 oxazoline) (PMOXA) and hydroxybenzaldehyde (HBA) to create a graft copolymer (PGA-PMOXA-HBA) that mimics the boundary lubrication properties of SZP and hyaluronan. (Morgese et al., 2018) PGA-PMOXA-HBA is designed to bind to damaged articular cartilage to provide a boundary lubrication layer and prevent cytokine penetration into the tissue. Tested in a rolling-ball-on-disc configuration within the boundary lubrication regime, certain PGA-PMOXA-HBA formulations were able to reduce friction coefficients of damaged articular cartilage (around 0.14) to levels exhibited by healthy articular cartilage (less than 0.06).(Morgese et al., 2017) Furthermore, PGA-CPMOXA-HBA prevented chondroitinase ABC-mediated and collagenase-mediated digestion of GAGs and collagen, respectively.(Morgese et al., 2018) Another technique involved an interpenetrating polymer network (IPN) designed to mimic GAGs lost during osteoarthritis progression. IPN includes a GAG-inspired zwitterionic polymer 2-methacryloyloxyethyl phos-phorylcholine (pMPC) that is photopolymerized *in situ* and decreased friction coefficients in bovine articular cartilage by 24% relative to untreated controls in a pin-on-disc configuration under fluid-film lubrication mode.(Cooper et al., 2017) These and other lubricants can reduce friction at the cartilage interface, however comparing absolute values from each study is difficult because the testing modality and lubrication mode vary broadly. Furthermore, it is possible that achieving a clinically effective strategy may require an approach that focuses more specifically on boundary lubrication of articular cartilage.

Scaffolds

Articular cartilage synthetic scaffold design criteria tend to focus on mechanical properties; however, some scaffolds have been developed with greater emphasis on improving tribological properties (Table 2). In one study, biodegradable polyvinyl alcohol (PVA) polymer hydrogels were functionalized with a carboxylic acid derivative boundary lubricant molecule and reduced friction coefficients up to 70% relative to unfunctionalized PVA scaffolds.(Blum and Ovaert, 2013) Furthermore, functionalized PVA hydrogels demonstrated friction coefficients that resembled those of native cartilage. Friction tests were conducted in a ball-on-disc configuration within the boundary lubrication mode. PVA/ polyvinyl pyrrolidone (PVP) blend hydrogels have also been tested against articular cartilage across lubrication modes and demonstrated average coefficients of friction between 0.12 and 0.14, which were close to cartilage-on-cartilage interaction (0.03) and much lower than cartilage-on-stainless steel articulation (0.46).(Kanca et al., 2018b) Interestingly, increasing hydrogel compressive modulus was highly correlated to coefficient of friction, likely due to lower congruence in stiffer hydrogels.

In a combinatorial approach, infiltration of a 3D-woven polycaprolactone scaffold with an alginate/polyacrylamide hydrogel created a composite scaffold that significantly reduced the boundary lubrication coefficient of friction from 0.64 for the scaffold alone to 0.28.(Liao et al., 2013) A tissue-engineered cartilage implant that replicates NeoCart® demonstrated a decreasing boundary mode coefficient of friction throughout 7 weeks of culture (0.40 at week 0 to 0.24 at week 7).(Middendorf et al., 2017) The coefficient of friction of constructs from week 3 of culture onward was not statistically different than healthy human cartilage (0.22) tested in the same pin-on-plate configuration using PBS as the test solution. This study is one of the first to assess the *in vitro* boundary lubrication tribological properties of an engineered articular cartilage product that has been investigated in a clinical trial. These characterizations are imperative for articular cartilage scaffolds that will be used *in vivo*.

Studying tribological properties for meniscal replacements is also of paramount importance. While hyaline articular cartilage has generally been a focus for scaffold strategies to improve diarthrodial joint lubrication, some scaffolds for meniscus replacement have also incorporated tribological properties as design criteria. Toward engineering lubrication in menisci, a silk fibroin scaffold that could potentially be used for meniscus replacement was developed. The friction coefficients of the scaffold tested against femoral cartilage (0.056) were significantly higher than native articular cartilage (0.014) and meniscus (0.021) controls tested against femoral articular cartilage.(Warnecke et al., 2017)

According to requirements for meniscus replacements described previously,(Rongen et al., 2014) a coefficient of friction of 0.056 for the scaffold against femoral articular cartilage could be within the range of acceptable tribological properties for meniscus replacements. (Warnecke et al., 2017) It should be noted that these values are dependent upon many factors such as the experimental setup, thus any comparisons to native tissue should only be made within the same testing modality, lubrication mode, and tissue type.

One meniscus replacement that was tested *in vivo* consisted of a porous polyurethane scaffold implanted into sheep to augment meniscus repair after partial meniscectomy. After 6 months *in vivo*, the boundary lubrication mode coefficient of friction of engineered meniscus (~0.35), tested in a pin-on-plate configuration, was not significantly different from either contralateral or adjacent healthy meniscus tissue, suggesting that the polyurethane scaffold was able to promote biomimetic neotissue formation.(Galley et al., 2011) Biomaterial scaffolds have been developed with coefficient of friction as a design criterion, but it is difficult to compare them to each other due to varying testing modalities. In general, the lack of meniscus tribology research is even more acute than for hyaline articular cartilage.

Bioactive factors

Bioactive factors, or molecules with an effect on cell behavior or extracellular matrix structure, that can enhance the tribological properties of native and engineered articular cartilages have been explored. Synoviocytes and superficial zone chondrocytes are known to endogenously produce SZP.(Peng et al., 2014) It has been demonstrated that TGF- β 1 increased SZP secretion in superficial zone chondrocytes seeded in monolayer, identifying it as a bioactive factor of interest.(Iwasa and Reddi, 2017) Combined treatment of synovium

explants with TGF- β 1 and bone morphogenetic protein 7 (BMP-7) further improved SZP secretion.(Iwakura et al., 2013)

An increase in SZP secretion does not always cause a decrease in tissue friction coefficients, as SZP must be retained at the cartilage surface to improve boundary lubrication.(Peng et al., 2016) To improve retention of SZP in engineered cartilage, native superficial zone cartilage extract, which likely contains binding macromolecules for SZP, was added to the culture media of self-assembled articular cartilage. Groups treated with a low concentration of extract demonstrated greater SZP staining and a boundary mode coefficient of friction of 0.03, which was significantly lower than the coefficient of friction of self-assembled cartilage cultured in the absence of superficial zone cartilage extracts (0.10).(Peng et al., 2016) Combining superficial zone extract with growth factors such as TGF- β 1 and BMP-7 could further enhance tribological properties.

Another growth factor of interest is insulin-like growth factor I (IGF-1). IGF-1 led to SZP localization at the surface of a collagen I gel seeded with meniscal fibrochondrocytes after 20 days in culture. This treatment resulted in a boundary friction coefficient of 0.22, which was not statistically different from the native tissue value of 0.2. Gels not stimulated with IGF-1, however, had a coefficient of friction of 0.29, which was significantly greater than the native tissue value.(Bonnievie et al., 2014) In another study, increasing the proportion of mesenchymal stem cells seeded with fibrochondrocytes led to a dose-dependent increase in SZP deposition on collagen I gels, which was matched by a decrease in coefficients of friction.(Bonnievie et al., 2016) The correlation between SZP deposition and coefficient of friction had an R^2 value of 0.80.

This suggests that MSCs not only produce SZP, but could produce SZP-binding factors that could be further investigated to improve SZP retention in native and engineered tissues. Bioactive factors to improve cartilage lubrication remain largely unexplored compared to bioactive factors used to improve other mechanical properties such as compressive moduli.

Mechanical stimulation

Mechanical stimulation, when applied at physiologic levels, has led to improvements in tissue-engineered cartilage lubrication. For example, a joint-mimicking loading system was applied to cell-seeded fibrin/hyaluronan composite gels. This biomimetic load increased SZP surface localization, suggesting enhancement of the construct surface, but quantitative tribological properties were not reported in this study.(Park et al., 2018) In a separate study, chondrocyte-seeded polyurethane scaffolds were subjected to dynamic compression and sliding surface motion by a ceramic ball, which also led to SZP localization at the surface of the construct. Additionally, constructs subjected to both sliding and compression exhibited a reduced coefficient of friction (0.251), compared to unloaded controls (0.681) and constructs only stimulated in compression (0.427).(Grad et al., 2012)

Hydrostatic pressure, known to increase collagen synthesis and tensile properties in self-assembled articular cartilage, has also been investigated as a mechanical stimulus to enhance cartilage tribological properties.(Murphy et al., 2013) Self-assembled constructs treated with TGF- β 1 and chondroitinase-ABC (C-ABC) were subjected to 10 MPa of continuous

hydrostatic pressure from days 10 to 14 of culture for 1 hr per day. These constructs demonstrated increased SZP staining compared to constructs stimulated with TGF- β 1 and C-ABC alone. Since coefficient of friction was not examined in this study, hydrostatic pressure as a method to improve tribological properties merits further investigation.

Supplementing culture media with factors found in synovial fluid, such as hyaluronan, can further replicate physiologic conditions during loading and have an impact on tribological properties. Indeed, mechanically stimulated, chondrocyte-seeded polyurethane scaffolds produced significantly more *PRG4* mRNA and SZP when culture medium was supplemented with hyaluronan.(Wu et al., 2017) This indicates that not only does hyaluronan have lubricating properties, but it also can regulate cellular behavior to promote better tribological properties. However, this study did not examine the functional impact of greater SZP content on construct tribological properties. These studies suggest that mechanical stimulation techniques should be further investigated toward improving lubrication of engineered constructs.

Perspectives

When articular cartilages are described, load-bearing capacity and nearly frictionless surfaces are presented as key characteristics. However, in many studies of tissue-engineered cartilages, mechanical properties are investigated while tribological properties are rarely explored. To augment the translatability of tissue-engineered cartilages, both mechanical and tribological functions should be considered as release criteria for cartilage implants. Because the FDA has guidelines for mechanical testing of engineered articular cartilages, we suggest that analogous guidelines be created for tribological properties.

Tissue-engineered articular cartilages must exhibit biomimetic mechanical properties, otherwise they will likely fail under repeated loads. *In vivo* durability is also of concern; therefore, tribological properties of engineered articular cartilages are also crucial because poor lubrication contributes to tissue degeneration.(Coles et al., 2010; Jay et al., 2007; Jia et al., 2016; Park et al., 2014) Indeed, if gross morphology, biochemical content, or mechanical properties are negatively impacted by insufficient lubrication, articular cartilages could degenerate in each of these aspects.

The tribological properties of native articular cartilages have yet to be defined, due to variability in testing conditions. A standardized tribological testing protocol, such as testing tissue bathed in PBS in a pin-on-plate configuration within the boundary lubrication regime, would be ideal to facilitate interlaboratory comparisons. If limitations exist that prevent adoption of this standardized assay, incorporating native tissue controls when performing tribological testing of engineered cartilages would provide a better indication of translational potential.

Of the two articular cartilages discussed in this review, the tribological properties of the knee meniscus remain relatively understudied, even though meniscus lubrication is vital for diarthrodial joint health. For example, a PubMed search for “knee meniscus tribology” returned 8 results, whereas a PubMed search for “articular cartilage tribology” returned 47

references. While this disparity is stark, both fields would benefit from increased research. A well-defined understanding of the tribology of native cartilages can provide design criteria for tissue-engineering efforts. Using that understanding to engineer clinically applicable implants should be the aim of cartilage researchers. Achieving biomimetic tribological properties in engineered articular cartilages will be crucial to the translational success of these approaches.

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Highlights:

- Loss of lubrication may harm morphology, biochemical, and mechanical properties of cartilage.
- Regulatory guidelines should include standardized tribology testing of neocartilage implants.
- Native tissue controls in tribology studies would better show translatability of neocartilages.
- Comprehension of synovial joints necessitates an increase in tribological characterization.
- A standardized tribology testing assay would facilitate interlaboratory comparisons.

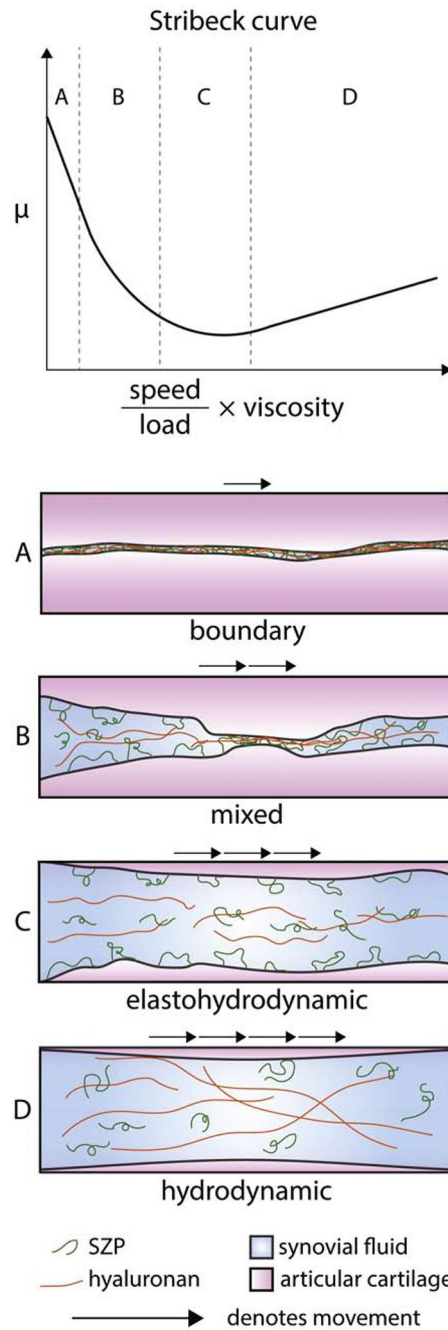


Figure 1: Lubrication regimes (A-D) within a synovial joint. The speed of articulation, magnitude of load, and fluid viscosity determine the mode of lubrication and affect the coefficient of friction (μ), as demonstrated in the Stribeck curve. Boundary lubrication (A) involves interaction of both articular surfaces resulting in a lack of fluid film. Mixed lubrication (B) combines aspects of boundary lubrication and fluid film lubrication. Elastohydrodynamic lubrication (C) is characterized by both a fluid film and deformation of articular cartilage. Hydrodynamic lubrication (D) involves a fluid film alone.

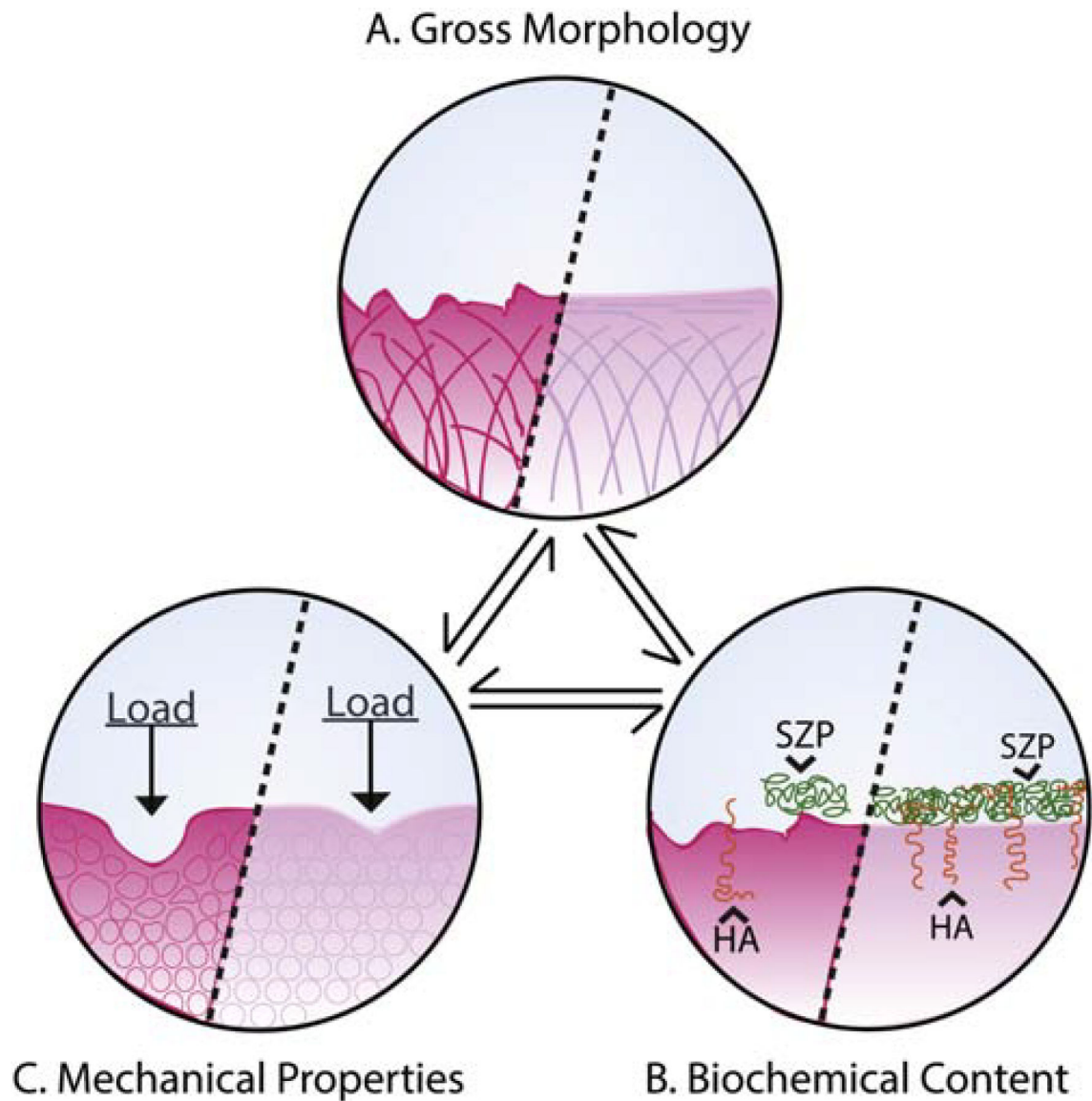


Figure 2:

A summary of how the gross morphology, biochemical content, and mechanical properties of cartilage feed into the maintenance of tribological function in the diarthrodial joint. In all panels, diseased cartilage is shown on the left and healthy cartilage is shown on the right. The gross morphology (A), biochemical content (B), and mechanical properties (C) of diseased cartilage (left) are compromised in comparison to healthy cartilage (right).

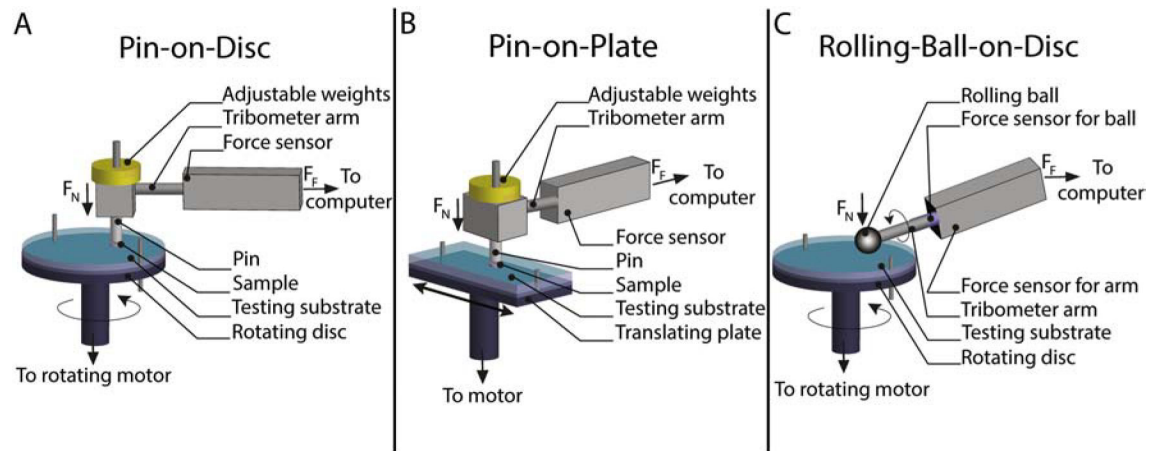


Figure 3:

Tribometer configurations. Schematic of a pin-on-disc tribometer (A) where a sample is glued to the pin and tested on a substrate attached to the rotating disc. Schematic of pin-on-plate tribometer (B), which uses a translating plate instead of a disc. Schematic of rolling-ball-on-disc tribometer (C), primarily used to test orthopedic implants, where both the tribometer arm and the disc can be rotated independently. In each setup, the coefficient of friction is calculated by dividing the friction force (F_F), obtained from the force sensor, by the known F_N created by the adjustable weights or the movement of the tribometer arm.

Table 1.Coefficients of friction (μ) for native articular cartilage and meniscus in the boundary lubrication regime

Tissue type	Species	Modality	Substrate	Lubricant	μ^*	Reference
AC	ovine	pin-on-plate	stainless steel	FBS	0.46	(Kanca et al., 2018b)
AC	ovine	pin-on-plate	AC	FBS	0.03	(Kanca et al., 2018b)
AC	human	pin-on-plate	glass	PBS	0.22	(Middendorf et al., 2017)
AC	porcine	pin-on-plate	glass	SF	0.001–0.11	(McCutchen, 1962)
AC	bovine	ball-on-disc	glass	N/A	0.19	(Blum and Ovaert, 2013)
AC	bovine	rolling-ball-on-disc	glass	PBS	0.12–0.16	(Jia et al., 2016)
AC	bovine	ball-on-disc	glass	N/A	0.121	(Grad et al., 2012)
AC	bovine	pin-on-plate	stainless steel	PBS	0.025	(Moore and Burris, 2015)
AC	bovine	pin-on-plate	glass	PBS	0.13	(Oungoulian et al., 2015)
AC	bovine	pin-on-plate	CoCr HC	PBS	0.15	(Oungoulian et al., 2015)
AC	bovine	pin-on-plate	CoCr LC	PBS	0.13	(Oungoulian et al., 2015)
AC	bovine	pin-on-plate	stainless steel	PBS	0.24	(Oungoulian et al., 2015)
AC	bovine	pin-on-disc	glass	PBS	0.069–0.13	(Peng et al., 2015)
AC	bovine	annulus-on-disc [†]	AC	PBS	0.24	(Schmidt et al., 2007)
AC	bovine	annulus-on-disc [†]	AC	BSF	0.028	(Schmidt et al., 2007)
AC	bovine	disc-on-disc [†]	AC	PBS	0.08	(Waller et al., 2013)
AC	bovine	disc-on-disc [†]	AC	CACP-SF	0.04	(Waller et al., 2013)
AC	bovine	disc-on-disc [†]	AC	HSL	0.03	(Waller et al., 2013)
AC	bovine	disc-on-disc [†]	AC	HSF	0.01	(Waller et al., 2013)
AC	bovine	disc-on-disc [†]	AC	CACP-SF+HSL	0.005	(Waller et al., 2013)
AC	bovine	pin-on-plate	AC	BSF	0.014	(Warnecke et al., 2017)
AC	bovine	pin-on-plate	glass	BSF	0.215	(Warnecke et al., 2017)
meniscus	bovine	pin-on-plate	glass	PBS	0.17–0.24	(Bonnievie et al., 2014)
meniscus	bovine	pin-on-plate	glass	PBS	0.20	(Bonnievie et al., 2016)
meniscus	bovine	pin-on-plate	glass	PBS	0.032	(Peng et al., 2015)
meniscus	bovine	pin-on-plate	AC	BSF	0.021	(Warnecke et al., 2017)
meniscus	bovine	pin-on-plate	glass	BSF	0.10	(Warnecke et al., 2017)
meniscus	ovine	pin-on-plate	glass	PBS	0.25–0.3	(Galley et al., 2011)
meniscus	ovine	pin-on-plate	glass	ESF	0.09–0.14	(Galley et al., 2011)

Abbreviations. AC: articular cartilage; BSF: bovine synovial fluid; CACP-SF: camptodactyly-arthropathy-coxa vara-pericarditis syndrome synovial fluid; CoCr LC: cobalt chromium low carbon; CoCr HC: cobalt chromium high carbon; ESF: equine synovial fluid; FBS: fetal bovine serum; HSF: human synovial fluid; HSL: human superficial zone protein; PBS: phosphate buffered saline; SF: synovial fluid;

* Boundary lubrication, average, equilibrium, kinetic coefficient of friction (μ)

[†] Tribological testing modalities analogous to pin-on-disc

Table 2.Coefficients of friction (μ) for engineered articular cartilage and meniscus in the boundary lubrication regime

Construct type	Species	Modality	Substrate	Lubricant	μ^*	Reference
cell-seeded AC scaffold (polyurethane)	bovine	ball-on-disc	glass	N/A	0.251–0.681	(Grad et al., 2012)
scaffold-free AC	bovine	pin-on-disc	glass	PBS	0.08–0.17	(Peng et al., 2014)
scaffold-free AC	bovine	pin-on-disc	glass	PBS	0.02–0.10	(Peng et al., 2016)
cell-seeded AC scaffold (collagen I)	human	pin-on-plate	glass	PBS	0.24	(Middendorf et al., 2017)
scaffold-free AC	leporine	pin-on-plate	glass	PBS	0.05–0.1	(Whitney et al., 2015)
scaffold-free AC	leporine	pin-on-plate	glass	PBS	0.05–0.38	(Whitney et al., 2017)
acellular AC construct (PCL scaffold with Alg/PAAm IPN hydrogel)	synthetic	pin-on-plate	Stainless steel	PBS	0.28	(Liao et al., 2013)
acellular AC hydrogel (PVA/PVP)	synthetic	pin-on-plate	AC	FBS	0.12–0.14	(Kanca et al., 2018b)
acellular AC hydrogel (PVA)	synthetic	ball-on-disc	glass	N/A	0.27–0.93	(Blum and Ovaert, 2013)
cell-seeded meniscus scaffold (collagen I)	bovine	pin-on-plate	glass	PBS	0.21–0.48	(Bonnievie et al., 2014)
cell-seeded meniscus scaffold (collagen I)	bovine	pin-on-plate	glass	PBS	0.15–0.33	(Bonnievie et al., 2016)
Acellular meniscus scaffold (collagen I)	synthetic	pin-on-plate	glass	PBS	0.38	(Bonnievie et al., 2016)
acellular meniscus scaffold (silk)	synthetic	pin-on-plate	AC	BSF	0.056	(Warnecke et al., 2017)
acellular meniscus scaffold (silk)	synthetic	pin-on-plate	glass	BSF	0.446	(Warnecke et al., 2017)
<i>in vivo</i> meniscus scaffold (polyurethane)	synthetic	pin-on-plate	glass	PBS	0.35–0.45	(Galley et al., 2011)
<i>in vivo</i> meniscus scaffold (polyurethane)	synthetic	pin-on-plate	glass	ESF	0.12–0.18	(Galley et al., 2011)

Abbreviations. AC: articular cartilage; Alg/PAAm IPN: alginate polyacrylamide interpenetrating network; BSF: bovine synovial fluid; ESF: equine synovial fluid; PBS: phosphate buffered saline; PCL: polycaprolactone; PVA: polyvinyl alcohol; PVP: polyvinylpyrrolidone;

* Boundary lubrication, average, equilibrium, kinetic coefficient of friction (μ)