# The Basic Science of Articular Cartilage: Structure, Composition, and Function

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rticular cartilage is the highly specialized connective tissue of diarthrodial joints. Its principal function is to provide a smooth, lubricated surface for articulation and to facilitate the transmission of loads with a low frictional coefficient (Figure 1). Articular cartilage is devoid of blood vessels, lymphatics, and nerves and is subject to a harsh biomechanical environment. Most important, articular cartilage has a limited capacity for intrinsic healing and repair. In this regard, the preservation and health of articular cartilage are paramount to joint health.

Injury to articular cartilage is recognized as a cause of significant musculoskeletal morbidity. The unique and complex structure of articular cartilage makes treatment and repair or restoration of the defects challenging for the patient, the surgeon, and the physical therapist. The preservation of articular cartilage is highly dependent on maintaining its organized architecture.

# STRUCTURE AND COMPOSITION OF ARTICULAR CARTILAGE

Articular cartilage is hyaline cartilage and is 2 to 4 mm thick. Unlike most tissues, articular cartilage does not have blood vessels, nerves, or lymphatics. It is composed of a dense extracellular matrix (ECM) with a sparse distribution of highly specialized cells called *chondrocytes*. The ECM is principally composed of water, collagen, and proteoglycans, with other noncollagenous proteins and glycoproteins present in lesser amounts.<sup>8,9</sup> Together, these components help to retain water within the ECM, which is critical to maintain its unique mechanical properties.



Figure 1. Gross photograph of healthy articular cartilage in an adult human knee.

Along with collagen fiber ultrastructure and ECM, chondrocytes contribute to the various zones of articular cartilage—the superficial zone, the middle zone, the deep zone, and the calcified zone (Figure 2). Within each zone, 3 regions can be identified—the pericellular region, the territorial region, and the interterritorial region.

#### Zones

The thin superficial (tangential) zone protects deeper layers from shear stresses and makes up approximately 10% to 20%

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Figure 2. Schematic, cross-sectional diagram of healthy articular cartilage: A, cellular organization in the zones of articular cartilage; B, collagen fiber architecture. (Copyright American Academy of Orthopaedic Surgeons. Reprinted from the *Journal of the American Academy of Orthopaedic Surgeons*, 1994;2:192-201 with permission.<sup>11</sup>)

of articular cartilage thickness. The collagen fibers of this zone (primarily, type II and IX collagen) are packed tightly and aligned parallel to the articular surface (Figure 2). The superficial layer contains a relatively high number of flattened chondrocytes, and the integrity of this layer is imperative in the protection and maintenance of deeper layers. This zone is in contact with synovial fluid and is responsible for most of the tensile properties of cartilage, which enable it to resist the sheer, tensile, and compressive forces imposed by articulation.

Immediately deep to the superficial zone is the middle (transitional) zone, which provides an anatomic and functional bridge between the superficial and deep zones. The middle zone represents 40% to 60% of the total cartilage volume, and it contains proteoglycans and thicker collagen fibrils. In this layer, the collagen is organized obliquely, and the chondrocytes are spherical and at low density. Functionally, the middle zone is the first line of resistance to compressive forces.

The deep zone is responsible for providing the greatest resistance to compressive forces, given that collagen fibrils are arranged perpendicular to the articular surface. The deep zone contains the largest diameter collagen fibrils in a radial disposition, the highest proteoglycan content, and the lowest water concentration. The chondrocytes are typically arranged in columnar orientation, parallel to the collagen fibers and perpendicular to the joint line. The deep zone represents approximately 30% of articular cartilage volume.

The tide mark distinguishes the deep zone from the calcified cartilage. The deep zone is responsible for providing the greatest amount of resistance to compressive forces, given the high proteoglycan content. Of note, the collagen fibrils are arranged perpendicular to the articular cartilage. The calcified layer plays an integral role in securing the cartilage to bone, by anchoring the collagen fibrils of the deep zone to subchondral bone. In this zone, the cell population is scarce and chondrocytes are hypertrophic.

#### Regions

In addition to zonal variations in structure and composition, the matrix consists of several distinct regions based on proximity to the chondrocytes, composition, and collagen fibril diameter and organization. The ECM can be divided into pericellular, territorial, and interterritorial regions.

The pericellular matrix is a thin layer adjacent to the cell membrane, and it completely surrounds the chondrocyte. It contains mainly proteoglycans, as well as glycoproteins and other noncollagenous proteins. This matrix region may play a functional role to initiate signal transduction within cartilage with load bearing.<sup>15</sup>

The territorial matrix surrounds the pericellular matrix; it is composed mostly of fine collagen fibrils, forming a basketlike network around the cells.<sup>21,48,54</sup> This region is thicker than the pericellular matrix, and it has been proposed that the territorial matrix may protect the cartilage cells against mechanical stresses and may contribute to the resiliency of the articular cartilage structure and its ability to withstand substantial loads.<sup>62</sup>

The interterritorial region is the largest of the 3 matrix regions; it contributes most to the biomechanical properties of articular cartilage.<sup>42</sup> This region is characterized by the randomly oriented bundles of large collagen fibrils, arranged parallel to the surface of the superficial zone, obliquely in the middle zone, and perpendicular to the joint surface in the deep zone. Proteoglycans are abundant in the interterritorial zone.

#### Chondrocytes

The chondrocyte is the resident cell type in articular cartilage. Chondrocytes are highly specialized, metabolically

active cells that play a unique role in the development, maintenance, and repair of the ECM. Chondrocytes originate from mesenchymal stem cells and constitute about 2% of the total volume of articular cartilage.<sup>2</sup> Chondrocytes vary in shape, number, and size, depending on the anatomical regions of the articular cartilage. The chondrocytes in the superficial zone are flatter and smaller and generally have a greater density than that of the cells deeper in the matrix (Figure 2).

Each chondrocyte establishes a specialized microenvironment and is responsible for the turnover of the ECM in its immediate vicinity. This microenvironment essentially traps the chondrocyte within its own matrix and so prevents any migration to adjacent areas of cartilage. Rarely do chondrocytes form cell-to-cell contacts for direct signal transduction and communication between cells. They do, however, respond to a variety of stimuli, including growth factors, mechanical loads, piezoelectric forces, and hydrostatic pressures.<sup>8</sup> Unfortunately, chondrocytes have limited potential for replication, a factor that contributes to the limited intrinsic healing capacity of cartilage in response to injury. Chondrocyte survival depends on an optimal chemical and mechanical environment.

#### Extracellular Matrix

In normal articular cartilage, tissue fluid represents between 65% and 80% of the total weight.<sup>46</sup> Collagens and proteoglycans account for the remaining dry weight. Several other classes of molecules can be found in smaller amounts in the ECM; these include lipids, phospholipids, noncollagenous proteins, and glycoproteins.

#### Water

Water is the most abundant component of articular cartilage, contributing up to 80% of its wet weight. Approximately 30% of this water is associated with the intrafibrillar space within the collagen, although a small percentage is contained in the intracellular space. The remainder is contained in the pore space of the matrix.<sup>35,63</sup> Inorganic ions such as sodium, calcium, chloride, and potassium are dissolved in the tissue water.<sup>29,30,33</sup> The relative water concentration decreases from about 80% at the superficial zone to 65% in the deep zone.<sup>9</sup> The flow of water through the cartilage and across the articular surface helps to transport and distribute nutrients to chondrocytes, in addition to providing lubrication.

Much of the interfibrillar water appears to exist as a gel, and most of it may be moved through the ECM by applying a pressure gradient across the tissue or by compressing the solid matrix.<sup>44,46</sup> Frictional resistance against this flow through the matrix is very high; thus, the permeability of the tissue is very low.

It is the combination of the frictional resistance to water flow and the pressurization of water within the matrix that forms the 2 basic mechanisms by which articular cartilage derives its ability to withstand significant loads, often multiple times one's body weight.

#### Collagens

Collagen is the most abundant structural macromolecule in ECM, and it makes up about 60% of the dry weight of cartilage. Type II collagen represents 90% to 95% of the collagen in ECM and forms fibrils and fibers intertwined with proteoglycan aggregates. Collagen types I, IV, V, VI, IX, and XI are also present but contribute only a minor proportion. The minor collagens help to form and stabilize the type II collagen fibril network.

There are at least 15 distinct collagen types composed of no fewer than 29 polypeptide chains. All members of the collagen family contain a region consisting of 3 polypeptide chains ( $\alpha$ -chains) wound into a triple helix. The amino acid composition of polypeptide chains is primarily glycine and proline, with hydroxyproline providing stability via hydrogen bonds along the length of the molecule. The triple helix structure of the polypeptide chains provides articular cartilage with important shear and tensile properties, which help to stabilize the matrix.<sup>33</sup>

#### Proteoglycans

Proteoglycans are heavily glycosolated protein monomers. In articular cartilage, they represent the second-largest group of macromolecules in the ECM and account for 10% to 15% of the wet weight. Proteoglycans consist of a protein core with 1 or more linear glycosaminoglycan chains covalently attached. These chains may be composed of more than 100 monosaccharides; they extend out from the protein core, remaining separated from one another because of charge repulsion. Articular cartilage contains a variety of proteoglycans that are essential for normal function, including aggrecan, decorin, biglycan, and fibromodulin.

The largest in size and the most abundant by weight is aggrecan, a proteoglycan that possesses more than 100 chondroitin sulfate and keratin sulfate chains. Aggrecan is characterized by its ability to interact with hyaluronan (HA) to form large proteoglycan aggregates via link proteins<sup>12</sup> (Figure 3). Aggrecan occupies the interfibrillar space of the cartilage ECM and provides cartilage with its osmotic properties, which are critical to its ability to resist compressive loads.

The nonaggregating proteoglycans are characterized by their ability to interact with collagen. Although decorin, biglycan, and fibromodulin are much smaller than aggrecan, they may be present in similar molar quantities. These molecules are closely related in protein structure; however, they differ in glycosaminoglycan composition and function. Decorin and biglycan possess 1 and 2 dermatan sulfate chains, respectively, whereas fibromodulin possesses several keratin sulfate chains. Decorin and fibromodulin interact with the type II collagen fibrils in the matrix and play a role in fibrillogenesis and interfibril interactions. Biglycan is mainly found in the immediate surrounding of the chondrocytes, where they may interact with collagen VI.



Figure 3. Extracellular matrix of articular cartilage. Two major load-bearing macromolecules are present in articular cartilage: collagens (mainly, type II) and proteoglycans (notably, aggrecan). Smaller classes of molecules, such as noncollagenous proteins and smaller proteoglycans, are present in smaller amounts. The interaction between the highly negatively charged cartilage proteoglycans and type II collagen provides the compressive and tensile strength of the tissue. (Reprinted with permission from Chen et al, 2006.<sup>13</sup>)

#### Noncollagenous Proteins and Glycoproteins

Although a number of noncollagenous proteins and glycoproteins are found within articular cartilage, their specific function has not been fully characterized. Some of these molecules (such as fibronectin and CII, a chondrocyte surface protein) likely play a role in the organization and maintenance of the macromolecular structure of the ECM.

## METABOLISM

In adults, the articular cartilage matrix is separated from the subchondral vascular spaces by the subchondral plate. Nutrition of the articular cartilage occurs by diffusion from the synovial fluid. The cartilage matrix restricts materials by size, charge, and molecular configuration. It is estimated that the average pore size within the ECM is approximately 6.0 nm.<sup>30,33,46</sup> Without a direct supply of nutrients from blood vessels or lymphatics, chondrocytes depend primarily on anaerobic metabolism.

Chondrocytes are responsible for the development, maintenance, and repair of the ECM via a group of degradative enzymes. Chondrocytes synthesize matrix components, including proteins and glycosaminoglycan side chains. The metabolic activity of the chondrocytes can be altered by a variety of factors within their surrounding chemical and mechanical environment. Proinflammatory cytokines (such as interleukin-1 and tumor necrosis factor– $\alpha$ ) have catabolic and anabolic effects that play a role in the degradation and synthesis of matrix macromolecules.<sup>9</sup>

Proteoglycans are synthesized, maintained, and secreted into the ECM by chondrocytes. A number of growth factors and regulatory peptides have been implicated in the regulation of proteoglycan metabolism, including insulin-like growth factors, transforming growth factor– $\beta$ , interleukin-1, and tumor necrosis factor– $\alpha$ . Very little is known about the molecular mechanism by which these growth factors and peptides elicit their effects on proteoglycan metabolism.

Chondrocytes are protected from the potentially damaging biomechanical forces by the surrounding ECM. A homeostasis of ECM metabolism balances the degradation of the different macromolecules with their replacement by newly synthesized products. Proteoglycan turnover can take up to 25 years,<sup>38</sup> whereas the half-life of collagen is estimated to range from several decades to up to 400 years.<sup>17</sup>

SPORTS HEALTH

The primary proteinases involved in cartilage turnover include the metalloproteinases (collagenase, gelatinase, and stromelysin) and the cathepsins (cathepsin B and D). Collagenase degrades native helical collagen fibrils at a single site. Gelatinase degrades denatured type II and type IV collagen; it also has significant activity against fibronectin, elastin, and collagen types V, VII, X, and XI.<sup>55,66</sup> The role of stromelysin is to degrade the protein core of aggrecan. All metalloproteinases are secreted as latent proenzymes that require activation extracellularly. Cathepsins are active in the degradation of aggrecan.

Joint motion and load are important to maintain normal articular cartilage structure and function. Inactivity of the joint has also been shown to lead to the degradation of cartilage.<sup>10</sup> Regular joint movement and dynamic load is important for the maintenance of healthy articular cartilage metabolism. The development of disease such as osteoarthritis is associated with dramatic changes in cartilage metabolism. This occurs when there is a physiological imbalance of degradation and synthesis by chondrocytes.<sup>64</sup>

## **BIOMECHANICAL FUNCTION**

Articular cartilage is a thin layer of specialized connective tissue with unique viscoelastic properties. Its principal function is to provide a smooth, lubricated surface for low friction articulation and to facilitate the transmission of loads to the underlying subchondral bone. Articular cartilage is unique in its ability to withstand high cyclic loads, demonstrating little or no evidence of damage or degenerative change.<sup>7,26,31</sup>

The biomechanical behavior of articular cartilage is best understood when the tissue is viewed as a biphasic medium. Articular cartilage consists of 2 phases: a fluid phase and a solid phase. Water is the principal component of the fluid phase, contributing up to 80% of the wet weight of the tissue. Inorganic ions such as sodium, calcium, chloride, and potassium are also found in the fluid phase. The solid phase is characterized by the ECM, which is porous and permeable.<sup>3,41,43</sup> The relationship between proteoglycan aggregates and interstitial fluid provides compressive resilience to cartilage through negative electrostatic repulsion forces.<sup>32,33,45</sup>

The initial and rapid application of articular contact forces during joint loading causes an immediate increase in interstitial fluid pressure. This local increase in pressure causes the fluid to flow out of the ECM, generating a large frictional drag on the matrix.<sup>18,33,34,41,43</sup> When the compressive load is removed, interstitial fluid flows back into the tissue. The low permeability of articular cartilage prevents fluid from being quickly squeezed out of the matrix.<sup>41,47</sup> The 2 opposing bones and surrounding cartilage confine the cartilage under the contact surface. These boundaries are designed to restrict mechanical deformation.

Articular cartilage is viscoelastic and exhibits time-dependent behavior when subjected to a constant load or deformation.<sup>68</sup> Two types of mechanisms are responsible for viscoelasticity in articular cartilage: flow dependent and flow independent.



Figure 4. A stress-strain diagram for articular cartilage during tensile loading. The schematic representations on the right illustrate the orientation of the collagen fibrils in response to loading. Reprinted with permission from Nordin and Frankel, *Basic Biomechanics of the Musculoskeletal System*.<sup>52</sup>

The flow-dependent mechanism depends on interstitial fluid and the frictional drag associated with this flow.<sup>3,43,44,60</sup> The drag resulting from the interstitial fluid is known as *biphasic viscoelastic behavior*.<sup>44</sup> The flow-independent component of viscoelasticity is caused by macromolecular motion specifically, the intrinsic viscoelastic behavior of the collagenproteoglycan matrix.<sup>23,69</sup> As a result, the fluid pressure provides a significant component of total load support, thereby reducing the stress acting upon the solid matrix.

Articular cartilage also exhibits a creep and stress-relaxation response. When a constant compressive stress is applied to the tissue, its deformation increases with time, and it will deform or creep until an equilibrium value is reached.43 Similarly, when cartilage is deformed and held at a constant strain, the stress will rise to a peak, which will be followed by a slow stress-relaxation process until an equilibrium value is reached. Because articular cartilage tends to stiffen with increased strain, it cannot be described by a single Young's modulus. Rather, the modulus of the tissue depends on the time at which the force measurement was taken during a stress-relaxation test, which was common practice in the preliminary studies of mechanical testing on articular cartilage.<sup>69</sup> The current method is to apply a known strain, which is immediately followed by a peak in measured force and a slow stress-relaxation process; the force/stress value is recorded when it has reached equilibrium. This process is repeated across a range of strain values, and the equilibrium modulus is calculated as the slope of the stress-strain curve.1,28,57

The complex composition and organization of cartilage through the middle zones of cartilage contributes significantly to its shear-resistant properties. Stretching of the randomly distributed collagen fibrils provides cartilage with its shear stress response<sup>24,58</sup> (Figure 4). The tensile force-resisting properties derive from the precise molecular arrangement of



Figure 5. A schematic depiction of the main components of articular cartilage when the tissue is unloaded (A) and when tensile load is applied (B). When the tissue is loaded, collagen fibrils align along the axis of tension. Reprinted with permission from Nordin and Frankel, *Basic Biomechanics of the Musculoskeletal System*.<sup>49,51</sup>

collagen fibrils. The stabilization and ultimate tensile strength of the collagen fiber are thought to result from the intra- and intermolecular cross-links (Figure 5).

# AGE AND DEVELOPMENT

Age determines the composition of the ECM as well as the organization of chondrocytes and their response to external factors such as cytokines.<sup>22</sup> With increasing age, there are zonal changes in the distribution of chondrocytes; however, the total number of chondrocytes remains essentially unchanged. Chondrocytes begin to dissipate in the superficial region, whereas the deeper layers have an increased number of cells.

With increasing age, there is a decrease in the hydration of the matrix, with a corresponding increase in compressive stiffness. This may have implications for the underlying subchondral bone, which may see increased forces as the cartilage loses its ability to undergo reversible deformation. Such changes may be noted on magnetic resonance imaging (MRI) as consolidation of trabeculae and subchondral sclerosis, which is often seen in association with a bone marrow edema pattern in the setting of cartilage degeneration. Preservation of a homeostatic ECM environment is critical to the maintenance of articular cartilage.

The size of proteoglycan aggregates within the ECM decreases with age. This may occur as a result of a decrease in the available binding sites of the HA chain or as the result of proteolytic damage to link proteins and their glycosaminoglycan chains. Aggregation may also affect pore size distribution and solute permeability. There is also an increased ratio of keratin sulfate to chondroitin sulfate. The

concentration of hyaluronan increases with age, but this results from the gradual accumulation of partially degraded hyaluronan rather than increased synthesis.<sup>36,37</sup>

## MRI IN ARTICULAR CARTILAGE

Noninvasive imaging techniques are an important tool for the evaluation, diagnosis, and monitoring of articular cartilage. MRI is widely accepted because of its ability to capture the integrity of soft tissue and subchondral cancellous bone. MRI is superior to conventional radiography and computed tomography because of its superior soft tissue contrast, multiplanar capabilities, and lack of ionizing radiation.

Standard MRI pulse sequences T1 and T2 use intrinsic relaxation times and are a reflection of the local tissue properties. T1-weighted spin echo sequences provide excellent anatomic detail and high contrast between cartilage and subchondral bone.<sup>25,27,53</sup> T2-weighted images capitalize on the arthrogram-like effect produced by the high signal intensity of joint fluid. T2 relaxation time is a reproducible and quantifiable parameter that reflects the internuclear dephasing that occurs as a result of transverse relaxation of the exited hydrogen dipoles. The collagen organization of the ECM may be measured using this technique.<sup>25,40,50,61,67,70,71</sup> On T1-weighted images, cartilage is higher in signal intensity than joint fluid; the opposite is true for the T2-weighted images.<sup>14,19,39,56,65</sup>

To assess the glycosaminoglycan content of articular cartilage, delayed gadolinium-enhanced MRI of cartilage may be used.<sup>4-6</sup> This method involves the intravenous injection of a negatively charged salt of a gadolinium magnetic resonance contrast agent, which in appropriate dosages acts to shorten T1 relaxation times. Tracking areas of depleted glycosaminoglycans are indirectly measured, and the use of delayed gadolinium-enhanced MRI of cartilage shows promise in its ability to detect injured or diseased articular cartilage.

Another imaging technique used to assess the proteoglycan content of articular cartilage is sodium MRI. When the excitational radio frequency is peaked on a specific sodium species (<sup>23</sup>Na), the relative fixed charge density of cartilage may be quantified, which is a function of the spatial resolution of charged proteoglycans.<sup>59</sup> However, lower sodium concentrations make clinical use of <sup>23</sup>Na difficult.<sup>20</sup>

The imaging of articular cartilage remains challenging owing to the zonal changes in structure and biochemical composition over a few millimeters. The potential for artifacts associated with MRI adds another dimension of complexity to this imaging dilemma.<sup>16</sup>

### SUMMARY

Articular cartilage is a highly specialized connective tissue of diarthrodial joints. Its principal function is to provide a smooth, lubricated surface for articulation and to facilitate the transmission of loads with a low frictional coefficient. The mechanical behavior of this tissue depends on the interaction of its fluid and solid components. The unique and complex structure of articular cartilage continues to make its treatment and repair a significant challenge.

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