

[Sports Physical Therapy]

Articular Cartilage Changes in Maturing Athletes: New Targets for Joint Rejuvenation

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Context: Articular cartilage has a unique functional architecture capable of providing a lifetime of pain-free joint motion. This tissue, however, undergoes substantial age-related physiologic, mechanical, biochemical, and functional changes that reduce its ability to overcome the effects of mechanical stress and injury. Many factors affect joint function in the maturing athlete—from chondrocyte survival and metabolism to structural composition and genetic/epigenetic factors governing cartilage and synovium. An evaluation of age-related changes for joint homeostasis and risk for osteoarthritis is important to the development of new strategies to rejuvenate aging joints.

Objective: This review summarizes the current literature on the biochemical, cellular, and physiologic changes occurring in aging articular cartilage.

Data Sources: PubMed (1969-2013) and published books in sports health, cartilage biology, and aging.

Study Selection: Keywords included *aging*, *athlete*, *articular cartilage*, *epigenetics*, and *functional performance with age*.

Study Design: Systematic review.

Level of Evidence: Level 3.

Data Extraction: To be included, research questions addressed the effect of age-related changes on performance, articular cartilage biology, molecular mechanism, and morphology.

Results: The mature athlete faces challenges in maintaining cartilage health and joint function due to age-related changes to articular cartilage biology, morphology, and physiology. These changes include chondrocyte loss and a decline in metabolic response, alterations to matrix and synovial tissue composition, and dysregulation of reparative responses.

Conclusion: Although physical decline has been regarded as a normal part of aging, many individuals maintain overall fitness and enjoy targeted improvement to their athletic capacity throughout life. Healthy articular cartilage and joints are needed to maintain athletic performance and general activities. Genetic and potentially reversible epigenetic factors influence cartilage physiology and its response to mechanical and injurious stimuli. Improved understandings of the physical and molecular changes to articular cartilage with aging are important to develop successful strategies for joint rejuvenation.

Keywords: articular cartilage; aging; athlete; exercise

Articular 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.^{1,26} 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.^{20,22} Together, these components help to retain water within the ECM, which is critical to maintain its unique mechanical properties. Along with collagen fiber ultrastructure and ECM, chondrocytes contribute to the secretion, organization, and maintenance of the ECM (Figure 1).

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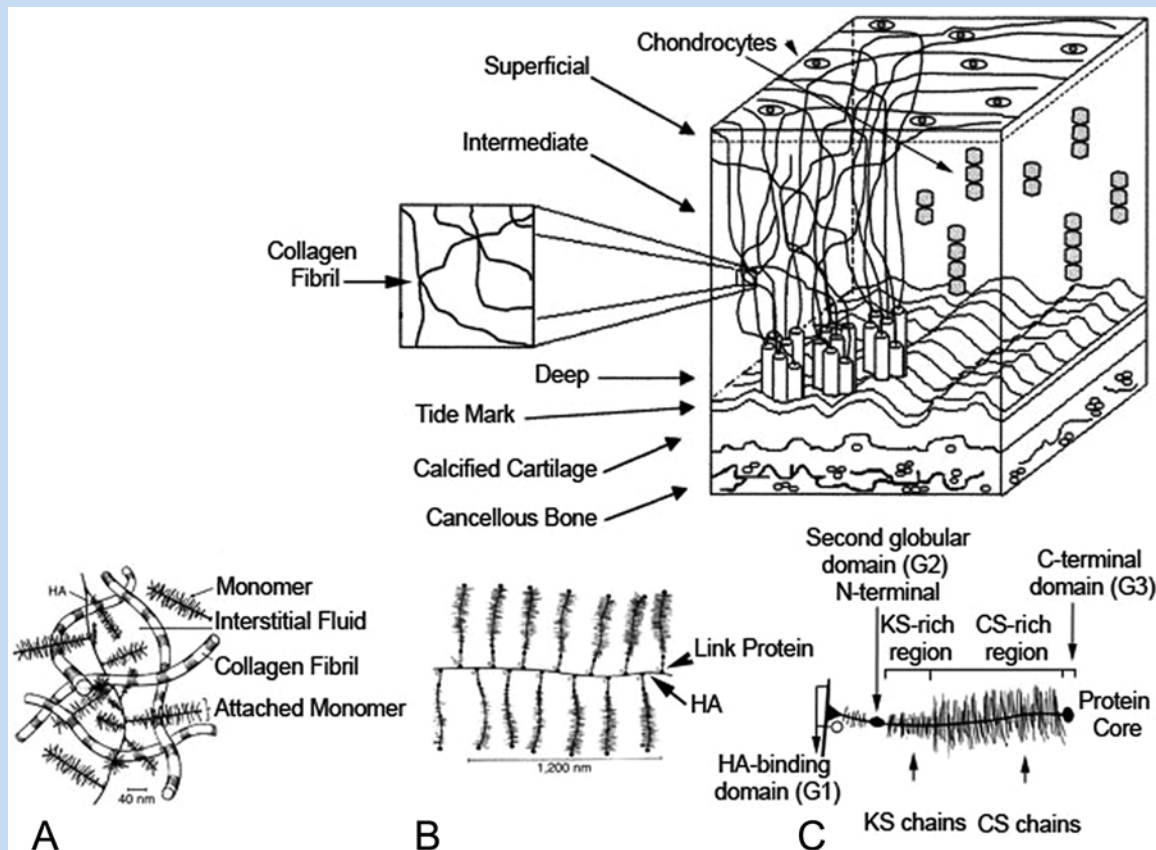


Figure 1. Organization of articular cartilage. Normal articular cartilage is composed of matrix, chondrocytes, and water. The matrix is principally composed of type II collagen fibers. Sulfated proteoglycans are linked to hyaluronate. (A-C) Structure of aggregating proteoglycans and their association with collagen. (A) Proteoglycans, chondrocytes, and water are trapped in a collagen fibril matrix. (B) Hyaluronic acid (HA) is a large polysaccharide composed of repeat glycosaminoglycans. (C) The glycosaminoglycans keratin sulfate (KS) and chondroitin sulfate (CS) attach to aggrecan, which in turn binds to HA via its N-terminal globular domain facilitated by link protein.^{27,99,120,132} Upper image reproduced with permission from Silver et al.¹²² Image A reproduced with permission from Mow and Hung.⁹⁹ Image B reproduced with permission from Mankin et al.⁸³ Image C reproduced with permission from Buckwalter et al.²¹

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.⁴ Chondrocytes vary in shape, number, and size, depending on the anatomic regions of the articular cartilage (Figure 1). 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 prevents ready migration to adjacent areas of cartilage. Chondrocytes are linked to the ECM and respond to a variety of stimuli, including growth factors, mechanical loads, piezoelectric forces, and hydrostatic pressures.^{20,142} Similarly, chondrocytes possess cell surface receptors for a variety of growth factors and cytokines, and they regulate both

anabolic and catabolic activities in response to these agents.¹³² Unfortunately, chondrocytes encapsulated within the dense ECM have limited room for replication, a factor further limiting the intrinsic healing capacity of articular cartilage.

Another tissue important to chondrocyte function and joint physiology is the synovium. While the cartilage is devoid of blood vessels, lymphatics, and nerves, the synovium is a vascularized connective tissue that contains specialized cells that produce fluid to lubricate and nourish articular cartilage (Figure 1). Changes to the synovium due to aging, inflammation, and disease can adversely affect chondrocyte metabolism and joint homeostasis.

DEFINITION OF AGE

Aging is defined as “a persistent decline in the age-specific fitness components of an organism due to internal

physiological degeneration.⁷¹¹² Most evolutionary biologists define aging as an age-progressive decline in intrinsic physiologic function, leading to an increase in age-specific mortality rate and a decrease in age-specific reproductive rate.^{40,93} According to the American Academy of Orthopaedic Surgeons, aging of joints occurs when (1) joint motion becomes more restricted and flexibility decreases with age because of changes in tendons and ligaments and (2) as the cushioning cartilage begins to break down from a lifetime of use, joints become inflamed and arthritic.¹

ARTICULAR CARTILAGE

Surprisingly few abnormalities are noted when considering the overall effect of aging on articular cartilage, which can remain intact for a lifetime. With advanced age, the cartilage may take on a yellowish discoloration, the nature of which is obscure. Cartilage appears to be thinner, but accurate measurements have not been systematically carried out to definitively support this concept. Histologically, no alterations are evident on light microscopy, but electron microscopic studies have suggested an increased number of cells showing organelle degeneration and intracytoplasmic fine filaments.¹⁰¹ Electron microscopic study of the collagen fibers shows increased fiber size in aging similar to that seen in osteoarthritis. Occasionally, giant fibers are seen, particularly in the deeper layers.¹⁰¹ A frequently encountered age-associated structural change in articular cartilage is increasing surface fibrillation.^{24,71} However, this does not necessarily lead to progressive articular cartilage degeneration.⁸⁷ As well, the frequency of advanced cartilage loss and osteoarthritis substantially increases with age. While the macroscopic changes are subtle in individuals who retain intact articular cartilage throughout life, studies have described a number of cellular and matrix changes associated with aging. These changes contribute to increased vulnerability of aging articular cartilage to injury and stress overload.^{39,65,117}

Chondrocyte Cellular Events and Function

There are fewer chondrocytes in the articular cartilage of older individuals.⁸⁵ Chondrocytes in aging individuals also show decreased functional activity. With fewer and less healthy chondrocytes to repair and maintain the matrix, previously healthy levels of loading may be greater than what the tissue can now tolerate. As such, there is greater risk for cartilage degeneration not just following injury or overuse but potentially even to normal activities.

Several reasons have been proposed for the age-related reduction in chondrocyte numbers. The ability of chondrocytes to proliferate and hence repair and maintain the cartilage matrix decreases with age.³ Programmed cell death may also play a role. Aging rats have higher levels of apoptotic chondrocytes in the calcified layer of knee cartilage.² Increased apoptosis in aging chondrocytes and reduced cellularity decrease the ability to repair and restore articular cartilage and result in lower functional capacity.^{13,74,128}

Loss of chondrocyte function with aging also occurs and represents an area where improved understanding of the mechanisms may reveal new opportunities for restorative therapy. There is progressive senescence of articular cartilage chondrocytes, as evidenced by increased expression of the cell senescence markers P16/INK4A and decreased telomere length with age.^{86,88,90,144} Cytoskeletal networks of old chondrocyte cells were also altered.³³ Aged chondrocytes had a different response to mechanical stimulation when compared with young and adult chondrocytes. Their viscoelastic properties are altered because of cell structure changes and cytoskeleton composition.³³

Insulin Growth Factor 1

Further evidence for chondrocyte senescence is the altered mitogenic response of aging cells to growth factors.¹⁰⁶ Insulin growth factor 1 (IGF-1) is an anabolic factor that can be synthesized locally in articular chondrocytes,³² and it initiates proteoglycan synthesis.⁴⁹ Furthermore, IGF-1 downregulates proteoglycan degradation induced by interleukin 1 α (IL-1 α).¹³¹ Aging articular chondrocytes show a decline in the responsiveness of the cells to IGF-1 and its downstream signaling pathway.^{80,89,95}

Transforming Growth Factor β

Members of the transforming growth factor β (TGF- β) superfamily, such as TGF- β 1, elicit chondrogenic properties and stimulate proteoglycan synthesis by articular chondrocytes.⁵⁶ Furthermore, TGF- β 1 can counteract the suppression of cartilage proteoglycan synthesis induced by IL-1 α .^{108,118} Aging articular chondrocytes show a decline in glycosaminoglycan synthesis and composition as a result of a lack of responsiveness of the cells to TGF- β 1 and its downstream signaling pathway.⁵⁶ Other key regulators that belong to the TGF- β superfamily are bone morphogenetic proteins and osteogenic protein 1 (OP-1). Both are important anabolic factors that enable homeostasis and repair of the cartilage.^{41,72} A remarkable decline in OP-1 expression level and function was found in individuals aged 35 to 75 years.²⁸

Molecular Changes

Other mediators of chondrocyte senescence that are associated with aging cells include reduced expression of the telomeric proteins that aim to maintain telomere function,¹⁴³ XRCC5 (x-ray repair complementing defective repair in Chinese hamster cells 5) that repairs DNA double-strand breaks,^{129,130} and sirtuin 1 that prevents growth arrest and apoptosis via P53 cascade.⁴⁸ Aging-related loss of the chromatin protein high-mobility group protein B2 (HMGB2) in articular cartilage was linked to reduced cellularity of cartilage.¹²⁸ Chondrocyte-downstream signaling (eg, protein kinase and caveolin) also is altered as a result of age.⁸²

Whatever the reason may be—telomere erosion, oxidative stress, or both—chondrocyte senescence is an essential component in cartilage physiology and ultimately leads to changes in the matrix.⁸⁵ Aged chondrocytes characteristically

have decreased functional activity. Along with that is the ECM protein synthesis and reduced responsiveness to anabolic growth factors.⁸⁸ They also produce fewer link proteins and smaller and less uniform aggrecan.⁸⁵

Extracellular Matrix

The major matrix proteins in cartilage are proteoglycans and collagen. Aggrecan is the key proteoglycan responsible for the resiliency of the tissue, while type II collagen provides tensile strength.¹¹⁴ Structural changes due to aging in any of the articular cartilage components contribute to a loss of tensile strength and joint stiffness.¹³⁹

Collagen

Collagen is the most abundant structural macromolecule in ECM, and it makes up about 60% of the dry weight of cartilage. It is organized in fibrils and fibers intertwined with proteoglycan aggregates. The triple helix structure of the collagen polypeptide chains provides articular cartilage with important shear and tensile properties, which help to stabilize the matrix.⁹² Type II collagen is the predominant collagen in articular cartilage. Collagen type II is more abundantly expressed in young cartilage rats than in older rats.⁹⁶ Nevertheless, there is very little turnover of type II collagen network (which has a half-life over 100 years) in healthy cartilage.¹³⁴ However, over time, an increase in cross-links between adjacent fibrils has been described. An increase in the number of bonds between collagen fibrils⁷⁸ is associated with the age-related increased stiffness and brittleness of the articular cartilage.^{2,58} Little evidence regarding the levels of nonenzymatic glycations (Maillard reaction) of collagen over age is documented. However, Bank et al⁷ reported that the formation of nonenzymatic glycations (like pentosidine) of collagen with age results in stiffer and more brittle collagen fibrils.⁷

Proteoglycan

All hyaline cartilages are characterized by high content of proteoglycans, which consist of a protein core with one or more linear glycosaminoglycan chains covalently attached. These chains may be composed of more than 100 monosaccharides. They extend from the protein core and remain separated from one another because of charge repulsion (Figure 2). Of the proteoglycans, aggrecan is the largest in size and most abundant by weight. Aggrecan possesses many chondroitin sulfate and keratin sulfate chains that interact with hyaluronan to form large proteoglycan aggregates via link proteins (Figure 2).^{25,126} Aggrecan occupies the interfibrillar space of the cartilage ECM and provides articular cartilage with its osmotic properties, which are critical to its ability to resist compressive loads.¹²⁶ Age-related changes in size, structure, and sulfation of aggrecan affect cartilage resilience and hydration.⁴⁷

Size and structure. 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 hyaluronan

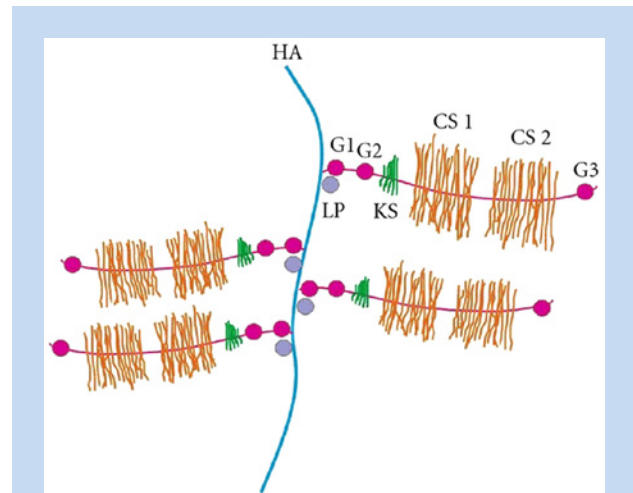


Figure 2. Schematic representation of the aggrecan structure. HA, hyaluronic acid; CS, chondroitin sulfate domain; KS, keratin sulfate; G, globular domain; LP, link protein.⁶³ Image reproduced with permission from Jerosch.⁶³

chain or as a result of proteolytic damage that enables the link between proteins and their glycosaminoglycan chains.^{8,97,98,126,135} Bolton et al^{15,16} were able to show that both protein expression and mRNA levels of link proteins decrease with age, and these changes are largely reflected by altered gene expression. Link proteins also undergo different degrees of glycosylation, but it is unclear if this is an implication of function and structure.⁹⁷ Furthermore, a notable increase in the heterogeneity of proteoglycan monomers was observed with age^{9,10,26,118} along with experiments showing an irregular aggregate structure in cultures of older chondrocytes.²⁶ Finally, proteoglycan monomers interact with hyaluronic acid via its protein core to form the macromolecular aggregates.⁵⁰⁻⁵⁴ Although the size of the aggregate depends partly on the size of the monomeric proteoglycans, it is determined by principally the length of the hyaluronic acid chain and number of monomers attached to it.⁵¹ Holmes et al⁵⁷ showed that the molecular mass of hyaluronic acid is not constant and that it decreases considerably (approximately 7-fold) during maturation and aging, thus suggesting that 2 factors regulate the size of proteoglycan aggregates in aging articular cartilage. Changes in aggregates are also associated with its hydration content.

Molecular composition of proteoglycans: Ratio of chondroitin sulfate to keratin sulfate. The glycosaminoglycan chains that are covalently bound to the core protein in the proteoglycans are long, unbranched disaccharide units. The 3 most common types of glycosaminoglycans are chondroitin sulfate, keratin sulfate, and dermatan sulfate. The negative charges attributed from the repeating sulfate and/or the carboxyl groups are important for the osmotic pressure and charged repulsive forces that maintain the structural integrity of articular

Table 1. Structure changes with age

Component	Aging Effect	Functional Change
Chondrocyte	Senescence: Decreased cellular activity Decreased absolute number of cells (apoptosis)	Reduced synthetic activity and repair
Extracellular matrix	Increased passive glycation Increase in the number of bonds between collagen fibrils	Increased stiffness and brittleness
	Changes in size, structure, and sulfation of aggrecans: Increase in ratio of proteoglycan keratan sulfate to chondroitin sulfate	Decreased resilience and hydration
	Decreased size of proteoglycan aggregates	Decreased hydration and cartilage resiliency
Water	Decrease in water content	Increased compressive stiffness

cartilage.^{23,27,115} In humans, increasing age is accompanied with a decreasing proportion of chondroitin sulfates in the ECM of nonosteoarthritic articular cartilage.¹² This change results in a decrease in the ratio of chondroitin sulfate to keratan sulfate. Since the elastic properties of cartilage are determined by the 3-dimensional organization and fixation of the charged groups (ie, mainly the chondroitin sulphate chains), a decrease in chondroitin sulfate will ultimately affect proteoglycan size.⁵⁹ Finally, Lee et al⁷³ studied aggrecan monomers and their glycosaminoglycan side chains using atomic force microscopy-based imaging and force spectroscopy. They showed that the decrease of chondroitin sulfate chains essentially transformed aggrecan into a linear core protein, with only traces of shorter keratan sulfate chains. These observations confirmed previous data showing that adult aggrecans are significantly weaker in compression based on these molecular changes.⁷³

Water content. Because of the hydrophilic nature of aggrecan's negatively charged sulfates, articular cartilage has about 70% to 80% water content attributing to its resilient properties.⁷⁵ Aggrecan has high affinity for water by virtue of its high negative fixed-charge density, and it is trapped in a 3-dimensional network of type II collagen fibrils.⁷ The hydrodynamic properties of aggregates determine the load-bearing capacity of articular tissue. As the electronegative charges of aggrecan draw water into the tissue, a large osmotic pressure is created that swells and expands the ECM. This pressure produces tension within the interlacing collagen network of the matrix; balance is achieved when tension in the collagen network prevents further entry of water.⁸⁴

Increasing age is accompanied by a decreasing proportion of chondroitin sulfates in the ECM of nonosteoarthritic articular cartilage.¹² Furthermore, the average size of proteoglycans decreases, impairing the ability of proteoglycans to aggregate spontaneously, all of which affect the hydration state of articular cartilage.⁷⁸

Summary

Age-dependent changes in articular cartilage increase the risk for cartilage degeneration and its ability to repair or regenerate itself. The synthetic activity of chondrocytes in all articular cartilage layers declines with age.⁶⁸ This decline leads to structural changes in the articular cartilage and its mechanical functions (Table 1). The decline in cellular activity in all articular cartilage layers can be associated with a decrease in the growth factor response and apoptosis of chondrocytes (Figure 3).^{2,78,113} This also decreases the ability of the cells to repair the tissue, counteract the catabolic mediators, and maintain homeostasis (Figure 3).

SYNOVIUM AND SYNOVIAL FLUID IN NORMAL AND AGED CARTILAGE

The term *synovium* refers to the soft tissue lining the spaces of diarthrodial joints, tendon sheaths, and bursae (Figure 4). When healthy, it is a thin layer of tissue that is only a few cells thick. The synovium includes the continuous surface layer of cells (intima) and the underlying tissue (subintima). The intima consists of macrophages and fibroblasts, while the subintima includes blood and lymphatic vessels. Between the intimal surfaces is a small amount of fluid, usually rich in hyaluronan (hyaluronic acid). Together, this structure provides a nonadherent surface between tissue elements.^{123,124}

Because articular cartilage is avascular, chondrocytes derive both oxygen and nutrition from the synovial fluid by simple diffusion.¹³² The synovium therefore acts to control the environment within joints. It does this in 2 ways: First, it serves as a membrane to determine what can pass into the joint space and what stays outside. Second, the cells within the synovium produce substances that lubricate the joint (Figure 4). Paracrine factors from the synovium have an important impact on cartilage metabolism.¹⁰¹ Systemic hormones that diffuse into the synovial

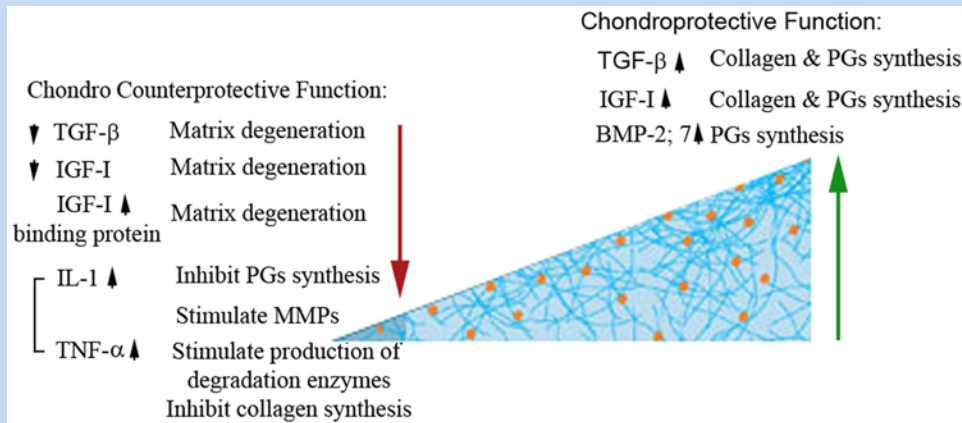


Figure 3. Anabolic versus catabolic changes in chondrocyte homeostasis. Autocrine, paracrine, and endocrine mediators manipulate chondrocyte cellular response in either anabolic or catabolic activity. TGF-β (transforming growth factor β), IGF-1 (insulin growth factor 1), and bone morphogenetic protein have anabolic activity on chondrocyte function and homeostasis. However, IL-1 (interleukin 1) and tumor necrosis factor α (TNFα), which are secreted from the synovial fluids, have the opposite catabolic effect on chondrocytes.¹³² Imbalance between these mediators can lead to cartilage degeneration and, ultimately, osteoarthritis.

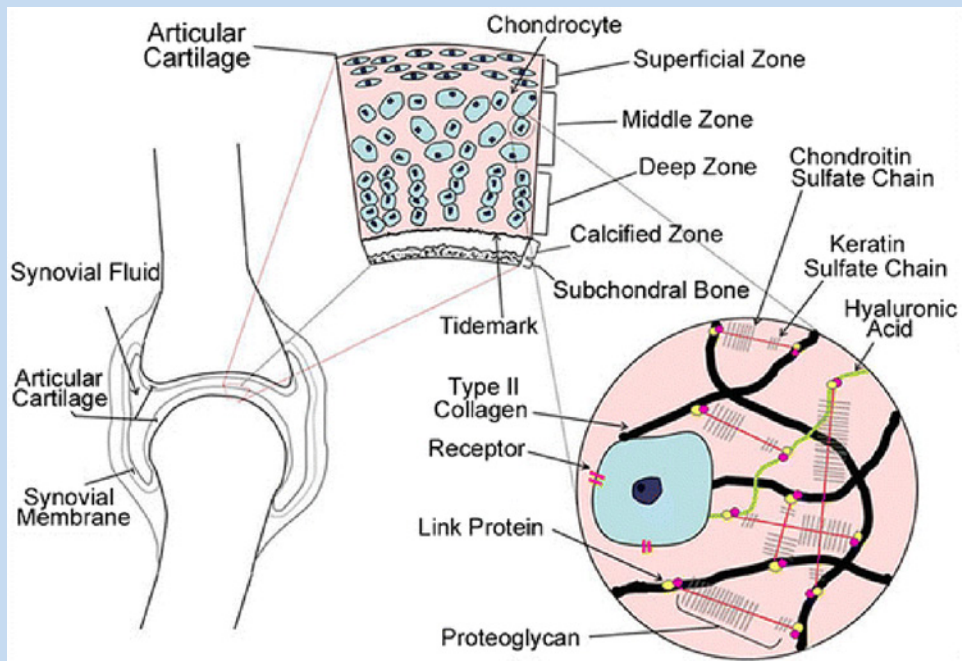


Figure 4. Schematic representation of articular cartilage, which is an avascular tissue with a heterogeneous composition. Chondrocytes exist in a depth-dependent arrangement based on cell size and shape. Cells in the tangential zone are aligned parallel to the articular surface, cells in the middle zone are spherical and randomly distributed, and cells in the deep zone are aligned perpendicular to the tidemark and calcified zone and integrate with the subchondral bone. The matrix consists of a network of type II collagen fibers, reinforced by cross-links formed among chains of hyaluronic acid, proteoglycans, and other noncollagenous proteins.¹⁴¹ Image reproduced with permission from Wescoe et al.¹⁴¹

fluid also influence articular chondrocyte metabolism.¹⁰¹ Thus, the health of the synovium factors significantly into joint and cartilage homeostasis. Changes due to aging can compromise joint performance and its response to loading and injury.

Synoviocyte Cellular Events and Function

In general, 2 types of cells are found: synoviocytes type A and type B. Type A cells are greater in number and contain vacuoles related to phagocytic function. Type B cells have a developed ergastoplasm and are capable of transforming into fibrocytes depending on the inflammatory response to coexistent cytokines. A wide array of cytokines are produced by synovial stimulation, including tumor necrosis factor, IL-1, IL-6, and IL-8; all play a role in the inflammatory process and tissue necrosis.¹¹

Synovium has various purposes, including an immune function, phagocytosis, lubrication, and cartilage nutrition. With regard to phagocytosis, synovium can remove bacteria and envelope small cartilage fragments that may result from joint overload, arthritis, or direct trauma. Elimination of intra-articular debris reduces the deleterious effect of inflammation over time.¹¹ Synovial lubrication is extremely important to the healthy joint by diminishing the joint frictional coefficient, reducing heat and wear.^{119,125} Hyaluronic acid, a deformable gel that increases elasticity as force is applied, is synthesized by type A synoviocytes. Joint forces promote the secretion of hyaluronic acid. The ability of synovial fluid to lubricate cartilage surfaces is also dependent on the presence of lubricin, a mucinous glycoprotein that is a product of megakaryocyte-stimulating factor gene expression. Loss of synovial lubricating ability has been implicated in the pathogenesis of degenerative joint disease.⁶²

It is difficult to describe age-associated changes in synovium and synovial fluid without describing the most relevant disease related to age. The following description of several changes is linked to common aging processes such as osteoarthritis.

Aging of Synovium and Synovial Membrane

With aging, the surface of the synovial membrane becomes more corrugated and sometimes folded into numerous villi in individuals older than 40 years.¹⁰⁴ The synovial villi, which provide versatile deformability during movement, become more common with age and may compensate for the growing inelasticity and increasingly fibrous character of the subintima.^{14,60} Morphologic studies of the aging synovium revealed an overall loss of synovium lining cells. Synovial intimal fibroblast numbers decrease with advancing age. In contrast, a relative increase in synovial intimal macrophages has been observed with age.¹⁰⁴ Moreover, fibrosis and decreased vascularity of the intimal layer are caused by collagen accumulation.⁶⁴ In older individuals, the number of fibroblasts, mast cells, and macrophages per unit were notably higher in the subintimal layer.¹⁰⁴ When microarthroscopy of human knee joints was analyzed for individuals over the age range of 15 to 56 years, there were generally more villi in aged individuals. In addition, the vascular network, cell distribution,

and profiles were less regular. Particular attention was paid to synovial lining cells, among which 3 main phenotypes could be recognized: synthetic type (present at all ages and hypertrophied in aged persons), macrophage-like (increasing with age), and fibroblast-like.¹⁰⁴ With age, blood vessels do not change in overall number; however, they tend to become more superficial, and their individual wall thickness increases.¹⁰⁴

Matrix Metalloproteinase

Aging is associated with elevation of advanced glycation end products in articular cartilage.¹³³ This increase in pentosidine has a strong correlation with a decrease in metalloproteinase-mediated tissue degradation.³⁰ The increased advanced glycation end products resulted in decreased cartilage degradation by metalloproteinases from synovial fluids, indicating that aged cartilage is less sensitive than young cartilage to metalloproteinase-mediated cartilage degradation.³⁰ This study was further confirmed in equine,¹⁷ showing that levels of active metalloproteinase 1 were lower in aged animals, unlike its activity in pathologic cases of osteoarthritis.

Prostaglandin E2 Synthesis

In response to acute inflammation induced by lipopolysaccharide, synoviocyte response to lipopolysaccharide can be measured by prostaglandin E2 levels.¹⁸ Young horses showed a drastic and significant increase in prostaglandin E2 concentration in synoviocytes, while older horses had less dramatic and lower prostaglandin E2 levels.¹⁸

Synovial Fluid

Hyaluronic acid plays an important role in joint lubrication and has beneficial effects on the joint tissues, including an anti-inflammatory effect, an inhibition of cartilage degeneration, and a positive role in cartilage repair.¹⁰⁰ Hyaluronic acid concentration gradually decreases in individuals between 40 and 70 years old.^{6,100} There is a direct relationship between age and the C6S:C4S ratio (ie, chondroitin-6-sulfate to chondroitin-4-sulfate).¹²¹ At 70 years, the concentrations of C6S and the C6S:C4S ratio decreased 48.4% and 35.4%, respectively, compared with those at 20 years of age.¹⁰⁰

Inflammatory Response

Inflammation is a part of the body's healing response. This response is stimulated by injury, infection, surgery, or allergic reactions. Normally, inflammatory response removes unhealthy and foreign material from the area. It also begins the repair process in which new blood vessels and tissue-rebuilding cells enter the injury site. Under healthy conditions, a normal inflammatory response (due to either acute traumatic loading or exposure to inflammatory insults) will activate chondrocytes and cells of the synovium and drive biochemical events that lead to the synthesis of proinflammatory mediators known to be destructive to joints (Figure 5).⁴³ IL-1 β and tumor necrosis factor α (TNF α) are prominent mediators of cartilage destruction.^{35,43,81,127} These proinflammatory cytokines are responsible for cartilage destruction and intracellular pathways

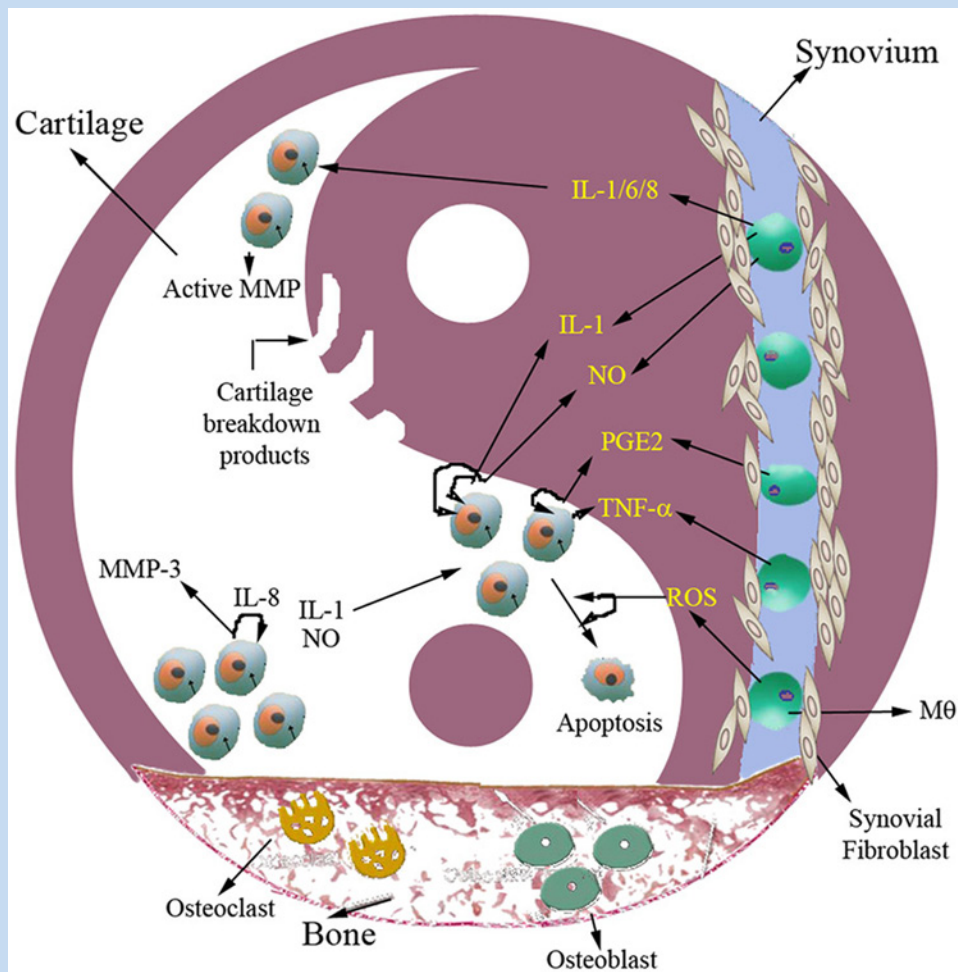


Figure 5. Crosstalk between chondrocyte and synoviocyte. Activation of signaling pathway either by mechanical injury or subinflammation produces cytokines, chemokines, and proteolytic enzymes that shift the homeostasis into a catabolic state. The expression of several matrix-degrading enzymes (metalloproteinase 1 [MMP-1], MMP-2, MMP-3, MMP-9, MMP-13) is increased and causes cartilage breakdown. Apoptosis seems to be mediated by proinflammatory mediators and reactive oxygen species. Aged chondrocytes have an insufficient response to growth factor and hence fail to restore the cartilage. The degradation pathway stays on, and continuation of matrix degradation leads to the development of osteoarthritis.

mediated by NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) and activator protein 1 that are involved in cytokine-mediated tissue destruction.⁸¹ Both can activate chondrocytes and synovial cells to produce IL-1 β , TNF α , IL-8, IL-18, and IL-6, as well as matrix metalloproteinases, nitric oxide, and prostaglandin E₂. Proinflammatory mediators also induce apoptosis and inhibit anabolic pathways (ie, the synthesis of proteoglycans, collagen type II, and tissue inhibitors of metalloproteinases). The induction of proinflammatory genes and the inhibition of matrix synthesis thus set up a self-sustaining inflammatory loop between synoviocytes and chondrocytes that exacerbates cartilage destruction.

Yin and Yang of Chondrocyte and Synoviocyte Function in Aging Joints

A low-grade inflammatory state is an integral part of the aging process and occurs at an earlier age in those who are overweight or obese.³⁷ Adipocytes, damaged organs, and/or tissue may serve as sources of cytokines. Low-grade infections may also result in chronic activation of the immune system, and this may predispose to a variety of chronic disease stages, including arthritis, which is well documented to be an age-related disease.^{29,37} While data are scant, it is possible that the ability to dampen inflammation following joint injury decreases with age. It is almost impossible to describe age-associated

changes in the articular cartilage without mentioning osteoarthritis. Changes within joint tissues affect repair and remodeling processes and predispose the joint to failure and the development of osteoarthritis when other factors are present, such as obesity, joint injury, and altered mechanics.

It appears that age-related changes in the ECM of cartilage result in a tissue that is less able to handle mechanical stress. The ability of the chondrocyte to maintain cartilage homeostasis declines with aging. This appears to be primarily due to decreased anabolic activity, although recent studies have shown an increase in catabolic responsiveness with age.⁴²

The lack of homeostasis in an aged joint leads to the progression of osteoarthritis.⁶⁷ Chondrocytes release chemoattractants such as IL-8 and monocyte chemoattractant protein 1 that direct the migration of leukocytes. Leukocytes, in turn, are a source of proinflammatory cytokines, such as IL-1 and TNF α , that induce apoptosis in chondrocytes (Figure 5). IL-1 can also induce chondrocytes to produce sufficient nitric oxide to cause cell death.¹⁰⁵ These proinflammatory cytokines upregulate the expression of intercellular adhesion molecule 1 on chondrocytes, which allows the attachment of leukocytes and facilitates the accumulation of toxic agents within the chondrocyte cytoplasm.¹⁰⁵ In addition, these cytokines stimulate the release of metalloproteinases by injured chondrocytes and leukocytes, and these metalloproteinases promote the degradation of the ECM.^{44,55,79,105} The resultant activation of signaling pathways, including reactive oxygen species generation, results in increased production of cytokines, chemokines, and proteolytic enzymes and induces chondrocyte apoptosis.⁴⁶ This catabolic response to injury serves to degrade the damaged matrix. Matrix degradation results in the release of growth factors stored in the matrix that would normally feed back on the cell and shut down the catabolic pathways (Figure 5). However, aged chondrocytes have an insufficient response to growth factor stimulation, resulting in continued matrix destruction from unbalanced catabolic and anabolic activity.⁷⁶

MATURING ATHLETE'S HEALING PROCESS IN RESPONSE TO VARIOUS TYPES OF INJURIES

Two major types of injuries should be considered in maturing athletes: prior injuries that accelerated joint degeneration and osteoarthritis and new injuries. Younger athletes experience traumatic injury to their ligaments and tendons.⁹⁴ The aging athlete's greatest menace is degenerative tissue. These are wear-and-tear disorders resulting from chronic overuse or trauma experienced over years of athletic stress.⁹⁴ DeHaven and Lintner³¹ reviewed the incidence of various athletic injuries with aging and found that inflammatory injuries increase until the age of 70 years. This raises a valid question: whether the aging athlete heals at a slower rate.³¹ Jackson and Rouse⁶¹ concluded that the presence of degenerative joints at the time of injury adversely affects the healing process, suggesting that the early treatment of injuries to prevent the development of degenerative changes at a later age.

Osteoarthritis

Many older athletes have trained from a very young age, making them vulnerable to osteoarthritis. Middle-aged athletes who participate in high-intensity physical loading are 8.5 times more likely to develop osteoarthritis of the hip than are age-matched controls.¹³⁶ Repetitive, high-impact loading results in cartilage microtrauma and degeneration of the weightbearing joints.⁶⁶ This effect may be exacerbated by previous injury or surgery, such as prior meniscectomy in the knee, which diminishes the ability of the joint to dissipate loads.

Epigenetics and Cartilage Physiology

Modifications of chromatin can change and affect transcription and regulation of genes. Methylation and/or histone modifications (acetylation, methylation, or phosphorylation) are described as epigenetic modifications that are heritable changes that affect transcription.³⁴ The methylation of sequences in or near regulatory elements can suppress gene expression through effects on DNA binding proteins and chromatin structure. Both increases and decreases in methylation occur with aging,^{34,109} depending on the tissue and the gene. These changes can have pathologic consequences, contributing to the development of malignancies and autoimmunity with aging and possibly to other disorders as well. Thus, while aging can affect DNA methylation, the changes in DNA methylation can affect aging.¹⁰⁹

In normal articular chondrocytes, most proteases are not expressed, probably because of silencing transcription via DNA methylation.¹¹⁰ However, osteoarthritic chondrocytes express a new set of genes involved in cartilage catabolism (metalloproteinases and a disintegrin and metalloproteinase with thrombospondin motifs).^{102,111} These enzymatic changes result in a loss of DNA methylation in the relevant promoter region. Furthermore, DNA methylation in chondrocytes are not the only age-related changes in DNA methylation, as inflammatory mediators such as IL β and TNF α produced by osteoarthritic chondrocytes can also affect DNA methylation.^{36,38,45,82,110} Age-related methylation of the OP-1 promoter may contribute to a decrease in OP-1 production in cartilage and a decrease in expression of OP-1-responsive genes, such as IGF-1, the IGF-1 receptor.⁷⁷ Adult mice develop osteoarthritis-like disease when nuclear factor of activated T cells transcription is changed. Nuclear factor of activated T cells specifically regulates the function of adult articular chondrocytes through its age-dependent expression, which is mediated by dynamic histone modifications.¹⁴⁰ Yet, expression levels of aggrecan in aged cartilage are not associated with DNA methylation.¹⁰⁷

CONCLUSION

Maturing athletes are at risk for compromised joint function due to degenerative changes accruing from past injuries as well as reduced ability to recover and repair from new injuries either due to stress overload or a catastrophic event.⁹⁴ This increased vulnerability is due to age-related changes (Figure 6)

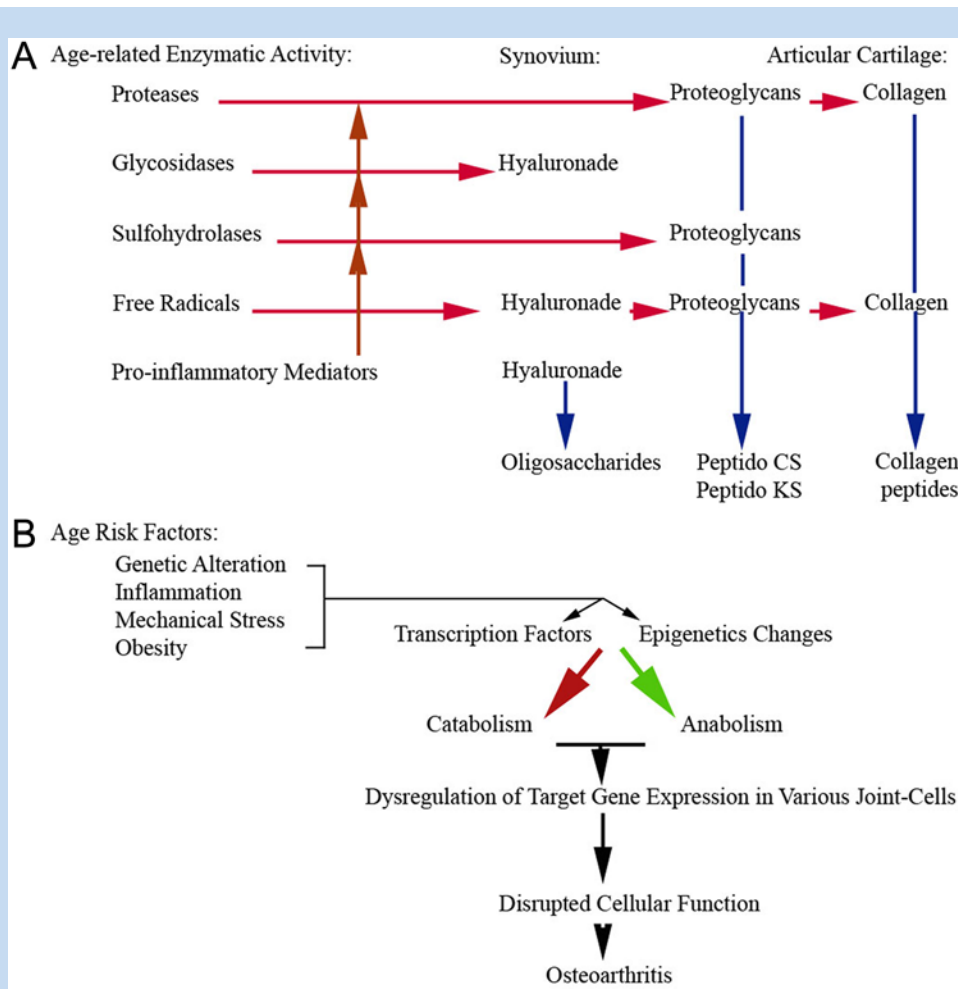


Figure 6. Summary of (A) age-related changes in gene expression and enzymatic activity and (B) the age risk factors that lead into these changes.

involving the individual as well as the joint—most notably, the articular cartilage, the synovium, and the interplay between these tissues.^{39,65,117}

The greatest threat to the health of the aging athlete is not the aging process itself but rather inactivity. Motion is critical to articular cartilage health, repair, and homeostasis. The application of constant compressive loading is important to maintain the normal structure of articular cartilage.^{19,69,91} Regular to moderate physical activity leads to improvements in the biomechanical and biological properties of articular cartilage⁷⁰ by acting as a chondroprotective agent,¹⁰³ increasing the synthesis and concentrations of proteoglycans and glycosaminoglycans⁷⁰ and the other components of cartilage matrix.^{137,138} As stated by Astrand,⁵ “there is less risk in activity than in continuous inactivity.” Maintaining joint health is critical to independent living and to maintaining health.

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