Cartilage Substitutes: Overview of Basic Science and Treatment Options

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Abstract

Articular cartilage defects that are symptomatic and refractory to nonoperative treatment represent a clinical management challenge. Although there have been important advances in stimulating intrinsic repair mechanisms, cartilage regeneration, and other substitution techniques, to date none has unlocked the understanding necessary to duplicate normal articular cartilage. The objectives of treatment of cartilage lesions are to obtain pain relief, reduce effusions and inflammation, restore function, reduce disability, and postpone or alleviate the need for prosthetic replacement. As the field of articular cartilage repair continues to evolve rapidly, the most appropriate treatment option for an individual patient should be based on the pathologic characteristics of the lesion and the patient's symptoms and expectations. The orthopaedic surgeon needs to be familiar with both the existing and the newly emerging cartilage treatment techniques in order to best educate patients and meet their expectations for long-term benefits.

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Articular cartilage is a unique tissue, and any substitute used to replace it is subjected to marked demands and stresses. Although a number of articular cartilage substitutes have been developed for treatment of chondral and osteochondral defects, to date none has successfully replaced normal articular cartilage. Patients who have isolated traumatic chondral and osteochondral defects in an area without surrounding degenerative articular cartilage have the most favorable results. While the natural history of isolated chondral defects is unknown,[1] it is assumed that these chondral and osteochondral defects may progressively enlarge with time and play a role in the development of more generalized osteoarthritic changes. The surgical goal is to replace these defects with cartilagelike substitutes so as to provide pain relief, reduce effusions and inflammation, restore function, reduce disability, and postpone or alleviate the need for prosthetic replacement.

Not all degenerative articular cartilage changes are symptomatic. However, osteoarthritis is one of the most common disorders of the musculoskeletal system, and the symptoms caused by it are among the most common reasons for patients to seek medical attention. Osteoarthritis is the leading cause of disability and impairment in middle-aged and older individuals,[2] entailing significant economic, social, and psychological costs. Each year, osteoarthritis accounts for as many as 39 million physician visits and more than 500,000 hospitalizations. By the year 2020, arthritis is expected to affect almost 60 million persons in the United States and to limit the activity of 11.6 million.[2]

Incidence of Cartilage Lesions

The total incidence of symptomatic and asymptomatic localized traumatic articular cartilage and osteochondral lesions is unknown. Clinically, the deleterious effect of an isolated traumatic impact to articular cartilage may take time to manifest, and the ability of standard radiography and magnetic resonance imaging to depict partial-

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thickness and smaller localized full-thickness lesions is limited. Even with arthroscopic examination, the traumatized area of articular cartilage may initially appear intact without obvious pathologic changes and then later degenerate. It has been proposed that 5% to 10% of all patients who present with acute hemarthrosis of the knee after a work- or sports-related traumatic event in fact have a full-thickness chondral injury.[3] In a retrospective review of 31,516 knee arthroscopies, chondral lesions were reported in 19,827 (63%) of the patients. On average, there were 2.7 articular cartilage lesions per knee, with unipolar grade IV injuries to the medial femoral condyle found in 1,729 (5%) of patients younger than 40 years of age.[4] The actual incidence of asymptomatic articular cartilage lesions in the contralateral knee of these patients and in asymptomatic individuals of the same age in the general population can only be inferred.

Basic Science

Developing a substitute for articular cartilage requires an understanding of its complex, highly ordered structure (Fig. 1). Cartilage is a viscoelastic material that exhibits a time-dependent behavior when subjected to a constant load. It provides the diarthrodial joint with a low-friction surface, allowing a smooth, gliding movement, and functions to transmit loads across the joint and to dissipate peak stress on the underlying subchondral bone.

A large percentage of extracellular matrix is composed of collagen, proteoglycans, and water, with only a sparse population of cells. In the matrix of mature articular cartilage, type II collagen fibers constitute 50% of the dry weight, and type V, VI, IX, X, and XI collagens are present in small amounts. The type II collagen exists in a triple-helix configuration (Fig. 2) that provides the tensile strength and mechanical integrity of cartilage and acts as a framework to immobilize and restrain the proteoglycans in the extracellular matrix.

Proteoglycans constitute 12% of the total weight of articular cartilage and are the major macromolecules occupying the interstices within the collagen fibrils. The glycosaminoglycans contain carboxyl groups and/or sulfate groups (keratan sulfate and chondroitin sulfate). The negative charge of the glycosaminoglycans is largely responsible for the high affinity for water displayed by the tissue, helping it to resist compressive loading. Moreover, the adjacent negatively charged branches of aggrecans repel each other, which allows them to occupy the largest possible domain. This, in turn, traps the proteoglycan within the collagen meshwork and contributes to stiffness and strength (Fig. 3).

Water makes up 65% to 80% of the total weight of articular cartilage, depending on the load status and the presence or absence of degenerative changes.[3] Through its strong affinity to the negatively charged proteoglycans, it helps resist very high compressive loads as it is being displaced. This resistance to loading depends on pressurization of water, and it is the pore size of the matrix, dictated by the concentration of proteoglycans, which determines the permeability of the tissue and its frictional resistance to flow. Water also contributes to joint lubrication and the transport of nutrients.

Chondrocytes occupy approximately 2% of the total volume of normal adult articular cartilage and are the only cell type therein. Their metabolism is affected by factors in their chemical and mechanical environment, such as soluble mediators (e.g., growth factors and interleukins), matrix composition, mechanical loads, hydrostatic pressures, and electrical fields. Due to the relatively low-oxygen-concentration environment in which chondrocytes exist, their metabolism is mainly anaerobic. Because chondrocytes synthesize all the extracellular matrix macromolecules (collagen fibrils, noncollagenous proteins, and proteoglycans) and degradative enzymes in normal articular cartilage, they are

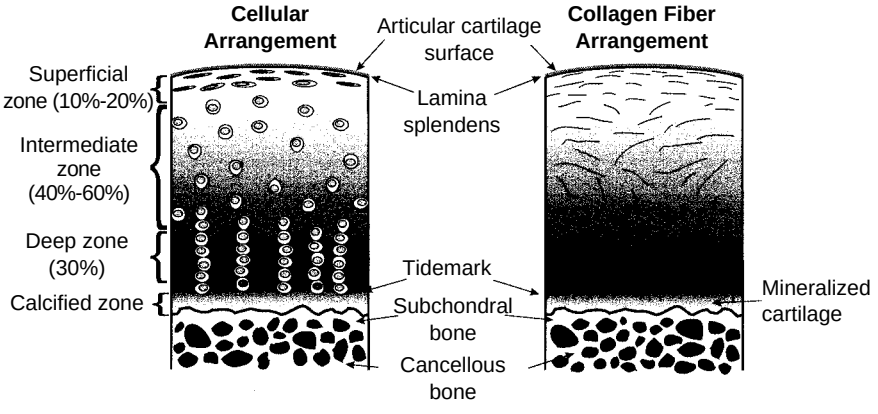

Figure 1 Major zones of cellular organization **(left)** and collagen fiber arrangement **(right)** in articular cartilage. Chondrocytes are elongated in the superficial tangential zone with their long axis aligned parallel to the surface. The chondrocytes gradually become rounded and are often arranged in columns; in deeper zones, they are completely surrounded by the extracellular matrix. (Adapted with permission from Mow VC, Proctor CS, Kelly MA: Biomechanics of articular cartilage, in Nordin M, Frankel VH [eds]: *Basic Biomechanics of the Musculoskeletal System*, 2nd ed. Philadelphia: Lea & Febiger, 1989, p 32.)

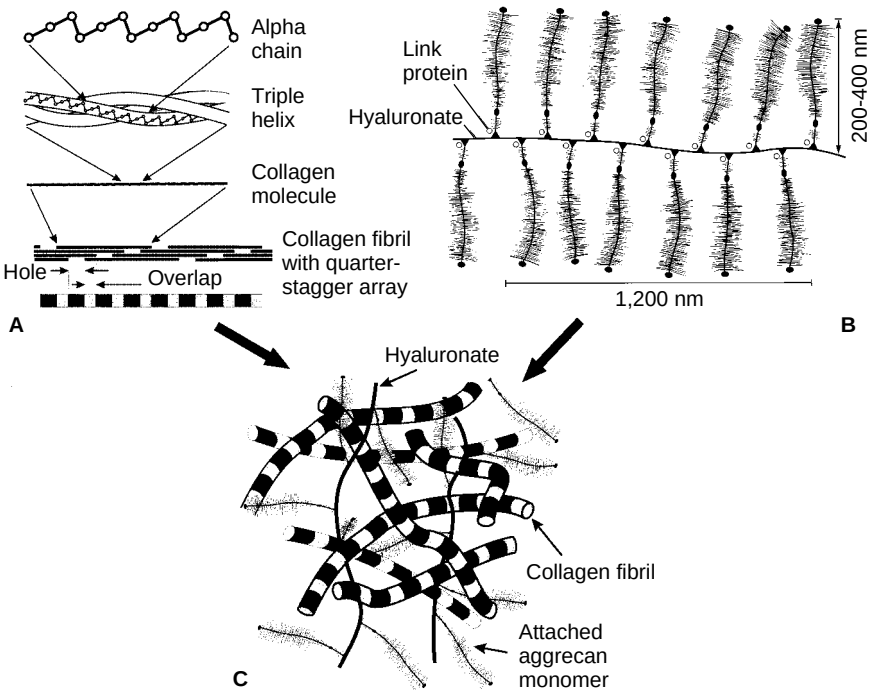

Figure 2 Formation of collagen fibrils. **A,** The triple helix is composed of three alpha chains forming a procollagen molecule (intracellular). Once outside the cell, the N- and C-terminal ends of the alpha chains are cleaved off, which allows fibril formation in a quarter-stagger manner. **B,** Aggrecan molecules attach to the hyaluronate backbone to form the proteoglycan aggregate. **C,** Matrix organization within articular cartilage. The meshwork of collagen fibrils entraps the proteoglycans. The underhydrated proteoglycans create a swelling pressure that keeps the network inflated. (Parts A and C reproduced with permission from Mow VC, Zhu W, Ratcliffe A: Structure and function of articular cartilage and meniscus, in Mow VC, Hayes WC [eds]: *Basic Orthopaedic Biomechanics*. New York: Raven Press, 1991, pp 143-198. Part B reproduced with permission from Simon SR [ed]: *Orthopaedic Basic Science*. Rosemont, Ill: American Academy of Orthopaedic Surgeons, 1994, p 10.)

important in directing cartilage remodeling and regeneration.

Embryologically, articular cartilage forms from mesenchymal cells that cluster together and synthesize a matrix. These cells become organized and can be recognized histologically as cartilage cells after the accumulation of a sufficient amount of matrix separates the cells and they acquire the characteristic spherical shape. This immature cartilage is considerably more cellular than mature tissue, with a higher number of cells per unit volume (Fig. 4). Besides being more cellular, this early cartilage tissue demonstrates abundant normal mitotic figures. Compared with articular cartilage in the adult animal, mitotic activity ceases with the development of a well-defined calcified zone (the tidemark) and, in some species, with closure of the epiphyseal plate. The lack of pluripotent cells within mature cartilage, with their ability to migrate, proliferate, and participate in a repair response, hinders the healing potential of articular cartilage. In addition, mature chondrocytes have only a limited ability to increase synthesis of the components of the surrounding matrix to repair tissue defects. There is a programmed cellular senescence, such that the capacity to synthesize some types of proteoglycans and increase cellular division in response to stimuli decreases with age.[5-7]

Cartilage Injuries and Repair

The long-term effects of a localized cartilage injury are dependent on chondrocyte and matrix survival. The extent of injury, the depth of the injury, and the location of the injury affect the eventual outcome (Fig. 5). Mechanical damage that results in injury only to the matrix components, not to the chondrocytes, has the potential that the surviving chondrocytes can synthesize new matrix and restore normal properties. However, if the mechanical destruction involves all components of the articular cartilage, including the chondrocytes, spontaneous repair to the damaged tissue is limited and does not duplicate normal articular cartilage. Each of these scenarios produces a different biologic and structural response. Trauma to articular cartilage beyond a critical level causes reduction in the viscoelasticity and stiffness of the cartilage. As a result, more force is transmitted to the subchondral bone, with consequent thickening and eventual stiffening of the subchondral plate. The increased stiffness of the subchondral bone allows more impact stresses to be transmitted to the cartilage, creating a vicious circle of cartilage degeneration and subchondral stiffening.

The thinnest zone of articular cartilage is the superficial zone, the so-called skin of articular cartilage, which acts as a barrier against the movement of molecules between the synovial fluid and the cartilage. This zone typically consists of two layers. MacConaill[8] described a bright layer at the articular surface visualized on phase-contrast study of articular cartilage and named it the "lamina splendens." This portion

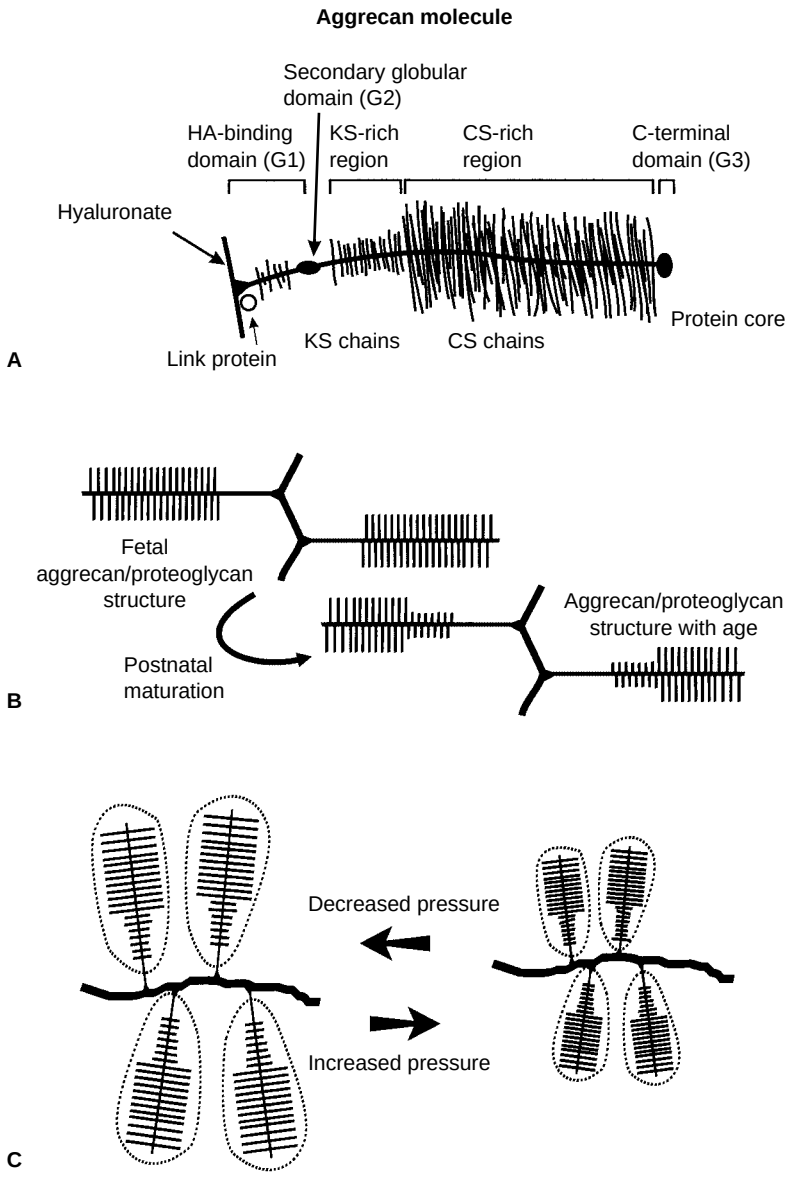

Figure 3 Component areas of the aggrecan molecule. **A,** The protein core has three globular domains (G1, G2, and G3) and specific areas containing the keratan sulfate (KS) and chondroitin sulfate (CS) glycosaminoglycan chains. Binding of the protein core to the hyaluronate (HA) molecule is specific; it occurs through the N-terminal globular domain and is stabilized by link protein. Numerous monomers of the aggrecan molecule can bind to the hyaluronate, forming a proteoglycan aggregate. These enormous structures are immobilized within the network of collagen. (Reproduced with permission from Simon SR [ed]: *Orthopaedic Basic Science*. Rosemont, Ill: American Academy of Orthopaedic Surgeons, 1994, p 9.) **B,** The change in structure of proteoglycans from fetal epiphyseal cartilage and mature articular cartilage. Fetal cartilage proteoglycan monomers are uniformly larger in size and length than the monomers in mature articular cartilage. (Reproduced with permission from Rosenberg LC, Buckwalter JA: Cartilage proteoglycans, in Kuettner KE, Schleyerbach R, Hascall VC [eds]: *Articular Cartilage Biochemistry*. New York: Raven Press, 1986, pp 41.) **C,** Pressure from loading of cartilage results in compression of the proteoglycan molecules, which provides increased resistance to loading compared with the normally extended molecule. (Reproduced with permission from Buckwalter J, Hunziker E, Rosenberg L, Coutts R, Adams M, Eyre D: Articular cartilage: Composition and structure, in Woo SL, Buckwalter JA [eds]: *Injury and Repair of the Musculoskeletal Soft Tissues*. Park Ridge, Ill: American Academy of Orthopaedic Surgeons, 1988, p 412.)

of the superficial zone covers the joint surface and corresponds to the adherent clear film that can be mechanically stripped from the underlying deeper portion of the superficial layer. It consists of fine fibrils with little polysaccharide and no cells.[5] Deep to this are the ellipsoid chondrocytes, which are aligned parallel to the articular surface. This deeper area has a high concentration of collagen and a low concentration of proteoglycans. The fibrils give this zone greater tensile strength than the deeper zones of articular cartilage.[9-11]

Removal of the superficial zone increases the permeability of the tissue and probably increases loading of the macromolecular framework during compression. It has been shown that disruption or remodeling of the dense collagenous matrix of the superficial zone is one of the first detectable structural changes in experimentally induced degeneration of articular cartilage.[12] This suggests that alterations in this zone may contribute to the development of osteoarthrosis by changing the mechanical behavior of the tissue. Furthermore, disruption of this zone could release cartilage molecules into the synovial fluid, which may stimulate an immune or inflammatory response. The lamina splendens and the underlying dense collagen fibril layer are an example of the site-specific organization of articular cartilage, which is difficult to duplicate with a substitute tissue or synthetic.

Articular cartilage is isolated from the marrow cells by the dense subchondral bone and does not have access to its vascularity. This lack of blood supply contributes to the inability to repair itself. The usual response to injury that occurs in other tissues throughout the body is dependent on hemorrhage, fibrin clot formation, and the mobilization of cells and important mediators and growth factors. Trauma that

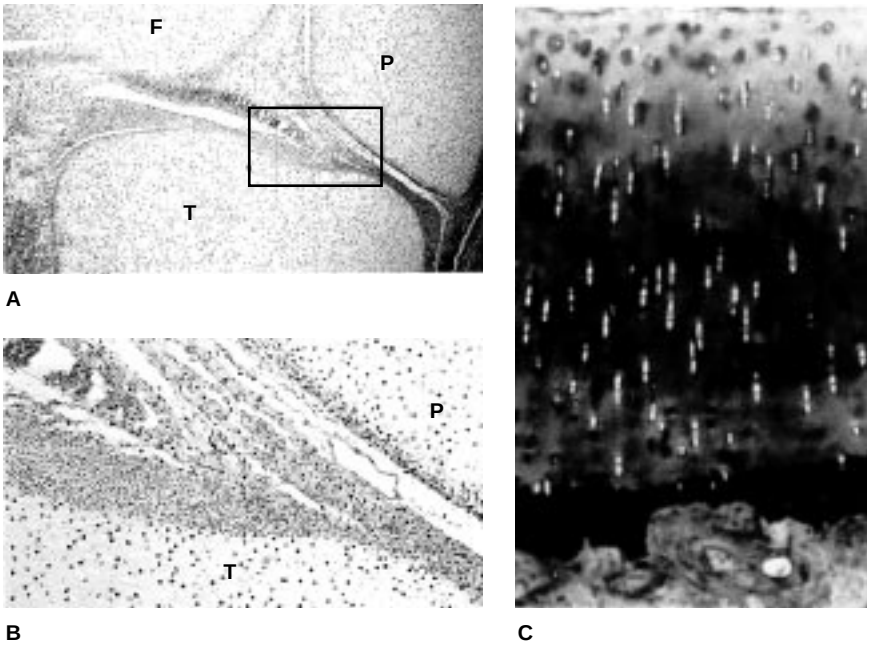

Figure 4 **A,** Histologic appearance of a human fetal knee joint (F = femur; P = patella; T = tibia)(hematoxylin-eosin, original magnification ×10). **B,** Higher-magnification view of area demarcated in **A** demonstrates an abundance of cells in lacunae in area where articular cartilage will form (hematoxylin-eosin, original magnification ×50). **C,** Histologic appearance of adult human articular cartilage (femoral condyle) (ruthenium hexamine trichloride, original magnification ×120). (Part C reproduced with permission from Hunziker EB: Articular cartilage structure in humans and experimental animals, in Kuettner KE, Schleyerbach R, Peyron JG, Hascall VC [eds]: *Articular Cartilage and Osteoarthritis*. New York: Raven Press, 1992, pp 185.)

significantly disrupts the chondrocytes and extracellular matrix but does not penetrate the subchondral bone has little or no capacity to heal.[13]

The only spontaneous repair reaction that occurs in superficial articular cartilage lesions is the transient proliferation of chondrocytes near the edges of the defect.[6] Similar cell clusters have been reported in the early stages of osteoarthritis and have been referred to as cell-clones.[14,15] Their size remains within constrained limits, and they do not proliferate significantly into the void of the lesion or produce adequate extracellular matrix (Fig. 6).[16]

In full-thickness and osteochondral lesions, when the subchondral plate is penetrated or removed, a reparative response is generated, which involves fibrin clot formation, cell migration from the bone marrow, and associated vascular ingrowth. Larger osteochondral defects are often filled with fibrocartilage, which is principally type I collagen.[17] Some rounded forms of chondrocytelike cells can develop and even synthesize type II collagen in certain portions of the defect. The repair tissue is usually intermixed with fibrous tissue, fibrocartilage, and hyalinized tissue. This reparative tissue differs from normal articular cartilage in that it is less organized, more vascular, and biochemically different in water content, proteoglycan content, and collagen type. Mechanically, the reparative tissue is less durable and is structurally different (Fig. 7).

For actual regeneration of articular cartilage to be accomplished, the cells present must become mature chondrocytes capable of restoring the biomechanical and structural integrity of the articular surface. Primitive mesenchymal cells retain the ability to differentiate into specific cell types depending on regulatory conditions (Fig. 8). These cells are found in the bone marrow, peripheral blood, perichondrium, periosteum, skin, muscle, and growth plate. They can become osteoblasts, fibroblasts, or chondroblasts depending on local and systemic stimuli. This population of cells naturally becomes reduced in number with age but can be grown in large numbers in cell culture. These cells can then be implanted in chondral and osteochondral defects, where they appear to have an enhanced potential for repair and regeneration. Ongoing research aims to induce the differentiation of these newly attracted or transplanted cells into mature chondrocytes, which will promote the formation of hyaline cartilage.

Growth factors are polypeptides that act in a paracrine manner and have a wide variety of regulatory effects on cells mediated by binding to cell surface receptors. Various factors have been identified, such as fibroblastic growth factors, platelet-derived growth factors, insulinlike growth factors, transforming growth factors (TGFs), and bone morphogenetic proteins (BMPs). These factors have an influence on cell functions, including migration, proliferation, and matrix synthesis and differentiation, depending on their concentration, the presence of cofactors, the type of target cell present, and the number of cell receptors available.

Bone morphogenetic proteins are characterized as members of the TGF superfamily (except BMP-1) because they have seven highly conserved carboxyl-terminal cysteines. More than a dozen members of the BMP family have been identified, all of which have different actions on specific types of bone-forming and cartilage-forming cells.[18] Types 2

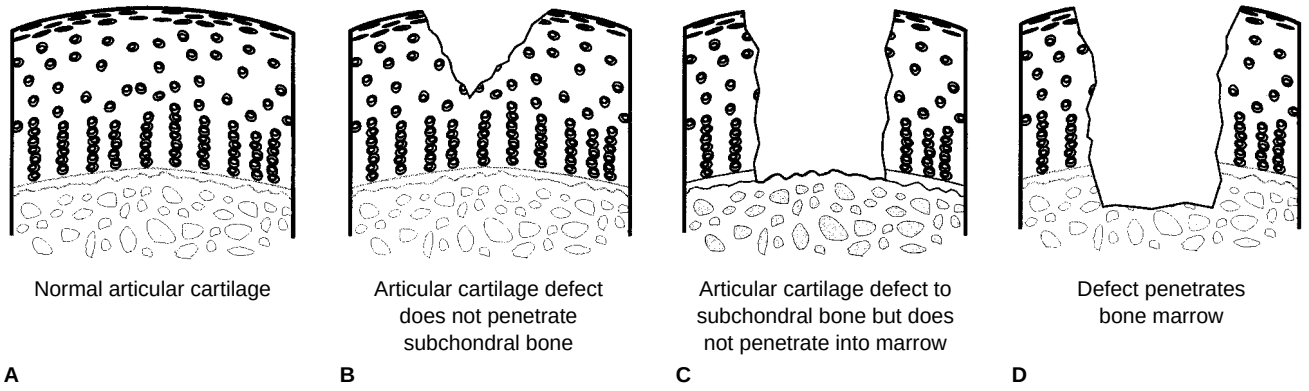

Figure 5 The various types and depths of articular cartilage defects or lesions that can be created in animal models to evaluate repair processes in articular cartilage. **A,** Normal articular cartilage is typically organized histologically into zones. **B,** A partial-thickness (superficial or shallow) defect penetrating to the middle zone is isolated from the blood supply and marrow space. Such a defect typically does not elicit or demonstrate a repair response. **C,** A lesion that penetrates to the subchondral bone but does not penetrate into the marrow space, if truly isolated from the marrow, will not repair. However, even a very small communication of the lesion with the marrow blood supply will elicit a repair response. Full-thickness lesions usually are in this category. **D,** A defect that penetrates through all zones of the articular cartilage and penetrates into the marrow space typically demonstrates a repair response that results in fibrocartilaginous tissue.

through 7, which have been found in extracts of demineralized bone, have the capacity to induce the formation of cartilage and bone at heterotopic sites.[18,19] Several studies have established a regulatory role for BMPs in the initiation of the differentiation of cartilage-forming and bone-forming cells from pluripotent mesenchymal stem cells.[20-24]

In particular, recombinant human BMP-2 (rhBMP-2) appears to be closely involved with the growth and differentiation of mesenchymal cells to chondroblasts and osteoblasts in developing limb buds.[25,26] There is also increasing evidence that these proteins have many influences on the differentiation and proliferation of cells in embryogenesis, depending on the presence of target cells and the prevailing environmental conditions.[25,27,28] In vitro studies in adults have shown that rhBMP-2 induces expression of cartilage and bone markers[29,30] and can enhance the production of articular cartilage matrix without inducing the formation of bone.[31-33] In vivo studies have also shown that rhBMP-2 can induce the formation of cartilage and bone at ectopic and skeletal sites.[34,35]

Sellers et al[36] investigated the effect of rhBMP-2 on the healing of full-thickness osteochondral defects in rabbits. The results showed greatly accelerated formation of new subchondral bone and improved histologic appearance of the overlying articular cartilage. At 24 weeks, the thickness of the healing cartilage was 70% of that of the normal adja-

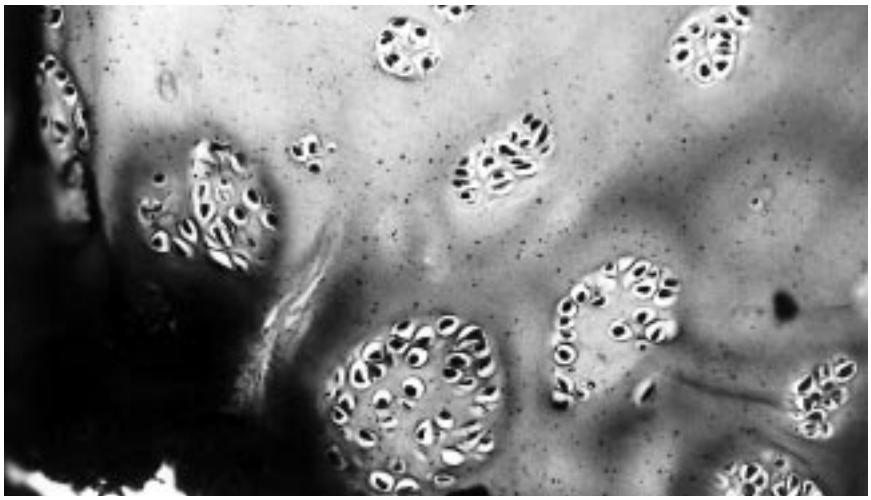

Figure 6 Chondrocyte cloning after articular cartilage transplantation in a goat model. Cloning of chondrocytes is usually observed at the margins of articular cartilage lesions or in cartilage demonstrating an attempted reparative response. They are believed to form in response to alterations in the articular cartilage matrix that signal the chondrocytes to proliferate or combine. The extracellular matrix they produce usually has properties different from those of normal articular cartilage (safranin O and fast green, original magnification ×63). (Adapted with permission from Jackson DW, Halbrecht J, Proctor C, VanSickle D, Simon TM: Assessment of donor cell and matrix survival in fresh articular cartilage allografts in a goat model. *J Orthop Res* 1996;14:255-264.)

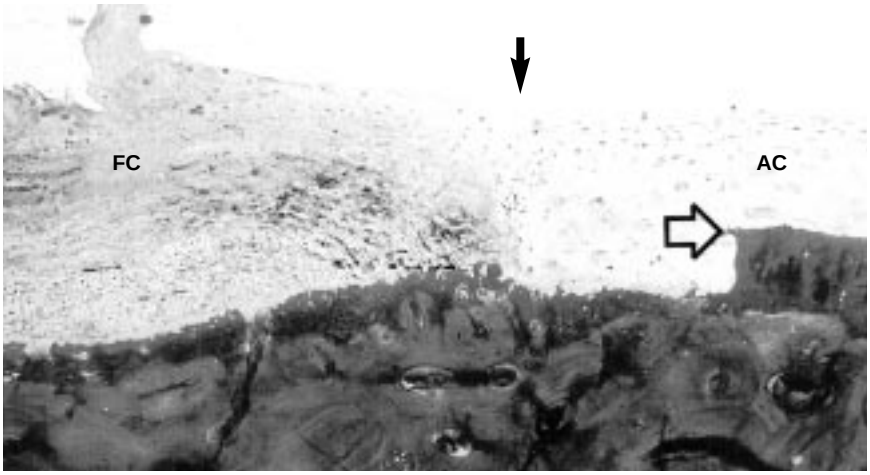

Figure 7 Development of fibrocartilage (FC) repair tissue in a marrow-penetrating articular cartilage lesion in the trochlear sulcus in a sheep model. The interface (solid arrow) between the original articular cartilage (AC) and the fibrocartilage appears integrated. A new subchondral bone plate has developed, but the tidemark has not developed to the original level (open arrow) at the 6-month postoperative interval (toluidine blue, original magnification ×10).

cent cartilage, and a new tidemark usually had formed between the new cartilage and the underlying subchondral bone. Immunostaining for type II collagen showed its diffuse presence throughout the repair cartilage in treated defects.[36]

Lietman et al[37] investigated the influence of rhBMP-7 on the synthesis, release, and maintenance of proteoglycans in explants of porcine articular cartilage held in chemically defined serum-free media. The authors found a 70% to 120% increase in synthesis after 7 to 10 days in culture and decreased release of proteoglycans from the explants of articular cartilage. Overall, there was a net increase in the proteoglycan content in extracts treated with BMP-7.[37]

The successful manipulation of the microenvironment to enhance or promote the synthesis of a replacement with characteristics similar to those of hyaline cartilage will require both extensive preclinical and clinical trials to establish its efficacy. The dose, method of delivery, timing of delivery, and distribution of the bioactive molecules throughout the matrices all affect the result. Any substitute will need to be stable under the loads and forces that articular cartilage is subjected to with the daily activities of living.

Stimulation of repair of superficial chondral lesions is more difficult because articular cartilage contains dermatan sulfate and other proteoglycans that confer antiadhesive properties on the surface of the cartilage. These hinder the ability of repair cells or tissue to bind to the lesion surface.[38-40] By first treating the surface of the defect with the enzyme chondroitinase ABC (which digests the antiadhesive proteoglycans) and then adding fibrin clot and mitogenic growth factors (particularly TGF-β1, or basic fibroblastic growth factor), increased coverage of a defect by mesenchymal cells from the synovium can be achieved.[17] This healing response generates a loose fibrous connective tissue, rather than cartilage. To date, this methodology has not created an articular cartilage substitute that is clinically applicable. Regeneration of the exact matrix composition and structure and restoration of the complicated interactions between chondrocytes and their matrix are the essential features necessary to biologically engineer articular cartilage substitutes.

Nonoperative Treatment Options

The vast majority of articular cartilage defects and degenerative articular cartilage changes do not cause symptoms or any significant disability. However, some patients with chondral and osteochondral lesions may present with complaints of pain, swelling, giving way, and mechanical symptoms of locking, catching, or crepitus. The pain and swelling are believed to be related to the presence of cartilage-breakdown products and the release of enzymes and cytokines. This combination cleaves articular cartilage and may produce painful synovitis and eventual further discomfort associated with capsular distention due to synovial effusion. Another source of symptoms is the stimulation of periarterial nerve fibers located in the subchondral bone. As sclerosis of the subchondral bone occurs, there may be secondary vascular changes in the bone that result in increased venous blood flow and congestion and further stimulation of the nerve fibers.

The immediate goal for the symptomatic patient seeking treatment of localized articular cartilage lesions is to decrease the secondary symptoms of pain and disability. Most symptoms related to articular cartilage lesions can be managed effectively with either conventional or alternative management modalities. These include patient education about the underlying process, as well as lifestyle and activity modifications. Weight reduction and spe-

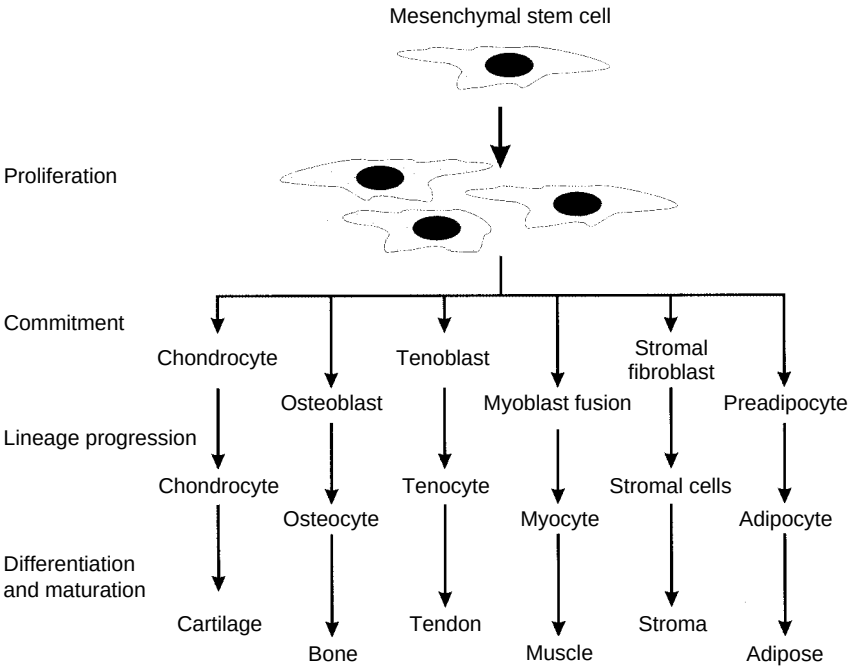

Figure 8 Potential lineage of mesenchymal stem cells. Once the cell is committed to a specific developmental pathway, it begins a differentiation process in which it no longer proliferates, but instead synthesizes unique components (e.g., extracellular matrix, cell surface receptors, bone, muscle) characteristic of the newly developing tissue these cells are targeted to make.

cific muscle-strengthening and nonaggravating fitness programs can also be helpful. The patient is usually receptive to treatments that minimize joint discomfort if the need for surgery is delayed or eliminated. Nonpharmacologic treatment of osteoarthritis includes application of heat and cold, selective use of bracing, physical therapy, and nonirritating aerobic conditioning. Pharmacologic therapies are more specific in their effects. These include mild analgesics; antiinflammatory drugs, such as cyclooxygenase-2 (COX-2) inhibitors; local corticosteroid injections; and chondroprotective agents, such as oral glucosamine and chondroitin sulfate and injectable hyaluronic acid for viscosupplementation.

Patients with osteoarthritis are looking for safer disease-altering treatments and are even exploring alternative therapies. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the medications most commonly prescribed for osteoarthritis. However, although more than 16 million individuals are now taking NSAIDs, there is no evidence that these drugs alter the natural history of cartilage degeneration. Furthermore, both patients and physicians are concerned about the possible long-term effects of NSAIDs. At least 16,500 deaths a year have been caused by gastrointestinal bleeding associated with NSAID usage.[41] The new COX-2 inhibitors are reported to have a lower rate of associated gastrointestinal bleeding side effects.

Viscosupplementation therapy for articular cartilage defects and degeneration by means of hyaluronic acid injections has been available in Europe for over a decade, in Canada since 1992, and in the United States since 1997. The use of viscosupplementation is based on the observation that there is a decrease in viscosity and elasticity of the synovial fluid in osteoarthritis and that the native hyaluronic acid in osteoarthritic knees has a lower molecular weight than that found in normal healthy knees. Replenishing the hyaluronic acid component of normal synovial fluid may play a role in supplementing the elastic and viscous properties of synovial fluid,[42,43] which may help relieve the signs and symptoms related to osteoarthritis and improve function. In vitro studies of human synoviocytes from osteoarthritic joints have revealed that exogenous hyaluronic acid stimulates de novo synthesis of hyaluronic acid,[44] inhibits release of arachidonic acid, and inhibits interleukin-1α–induced prostaglandin E_2 synthesis by human synoviocytes.[45] Recent clinical trials have evaluated the efficacy and safety of intra-articular hyaluronic acid injections.[46-50]

Overall, viscosupplementation often does not replace the need for some alteration of specific aggravating activities by means of muscle strengthening and weight reduction. However, it may decrease the medical costs and morbidity associated with NSAIDs by allowing patients to use less medication.[51,52] It represents an adjunct to current treatments for osteoarthritis and an alternative treatment when other forms of medical treatment are contraindicated or have failed.

There is a need for further studies to clarify the specific indications for the various nonoperative treatment modalities and to evaluate their effectiveness with randomized, controlled clinical trials. When evaluating both nonoperative and operative treatments, the placebo effect of treatments of osteoarthritis and cartilage lesions must be taken into consideration. Furthermore, symptoms secondary to articular cartilage lesions and osteoarthritis may have peaks and valleys independent of

treatment, and relief may not necessarily be due to the particular treatment rendered. For patients for whom nonpharmacologic or pharmacologic modalities have been unsuccessful, and for those who are unable or unwilling to take the medications, the utilization of surgical interventions can be considered.

Operative Treatment Options

There are a number of surgical options for the treatment of chondral and osteochondral defects that are refractory to nonoperative management. Each of these options has variable reported success rates depending on patient age and activity level and the location, size, shape, and depth of the defect. The techniques currently being most widely utilized clinically for cartilage defects and degeneration are not articular cartilage substitution procedures, but rather lavage, arthroscopic debridement, and repair stimulation. The direct transplantation of cells or tissue into a defect and the replacement of the defect with biologic or synthetic substitutes accounts for only a small percentage of surgical interventions at this time.

"Healing" related to articular cartilage is a rather nonspecific term. Healing has been defined as restoring the structural integrity and function of a damaged tissue. A biologic reparative process implies replacing the damaged or lost cells or matrix with new cells or matrix, but not necessarily restoring the tissue to its original structure. It is the term "regeneration" that implies that the damaged tissue has been replaced by tissue—specifically, new cells and matrix identical to the original tissue.[13] "Substitution" implies replacement of the damaged cartilage with biologic or synthetic polymers that possess mechanical properties similar to those of articular cartilage but does not necessarily require the exact duplication of normal articular cartilage.

Lavage and Debridement

Lavage and arthroscopic debridement are techniques that do not induce repair but instead are directed toward temporary relief of the symptoms and disability associated with articular cartilage lesions. Arthroscopic lavage has been reported to have beneficial effects on mild to severe osteoarthritis of the knee.[53-56] The benefit of arthroscopic lavage is believed to be due to the removal of degenerative articular cartilage debris, proteolytic enzymes, and inflammatory mediators. In addition to the benefits of lavage, arthroscopic debridement is believed to be helpful by virtue of removal of partially detached flaps or degenerative articular cartilage and contouring of the articular surface.[57-59] Because neither technique penetrates the tidemark or subchondral bone, there is no significant production of hemorrhage or clot formation. Consequently, there is no migration or proliferation of repair cells to the defect, and thus there is limited or no potential for further healing.

Repair Stimulation

The goal of repair stimulation (by means of drilling, abrasion arthroplasty, or microfracture) is to induce the migration of high concentrations of potential repair cells into the chondral or osteochondral defects. Various techniques for enhancement of the migration of marrow cells and hemorrhage have been developed (Fig. 9). The usual result of these penetrating techniques is the partial filling of the articular defect with fibrocartilage that contains principally type I collagen. Unlike the desired hyaline cartilage (which is principally type II collagen produced by the chondrocytes), this fibrocartilage has diminished resilience and stiffness, poor wear characteristics, and a predilection for deterioration over time.

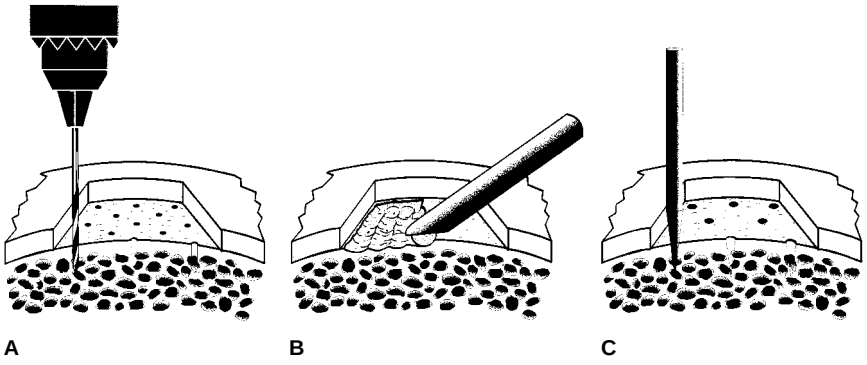

Figure 9 Various methodologies currently used to elicit repair tissue in articular cartilage defects. **A,** Current methods involve penetrating the underlying bone endplate by drilling, as proposed in the Pridie procedure. Variations include abrasion **(B)** and microfracture **(C)**. All these techniques penetrate the subchondral bone to open communication with a zone of vascularization to initiate fibrin clot formation and to obtain the potential benefit of vascular ingrowth or migration of more primitive mesenchymal cells from the bone marrow. These communications open the defect to the migration of many types of cells, including fibroblasts and inflammatory cells. These cells may compete with a limited number of the primitive mesenchymal cells to occupy the fibrin matrix, contributing to a variety of repair scenarios. These methods penetrate the subchondral bone plate and tidemark, but the intent is not to disrupt the integrity of the subchondral bone. Large disruption or removal of the subchondral bone endplate may result in detrimental mechanical, structural, and biologic changes.

Varying amounts of fibrous tissue, fibrocartilaginous tissue, and articular cartilage–like tissue have been reported to fill these defects after the use of penetrating techniques.[5] Microfracture studies in an equine model have suggested that type II collagen may predominate in the repair tissue from the fibrin clot, which may increase in amount over a period of 4 to 12 months.[60] Correction of any malalignment deformities and institution of an early-motion rehabilitation program have been reported to be beneficial in improving the quality of replacement tissue. Overall, this heterogeneous tissue has inferior mechanical characteristics, which leads to deterioration of clinical results with time. The outcomes have been particularly poor in cases of malalignment. These findings have stimulated the exploration of other treatment modalities that yield tissue that more closely simulates native cartilage.

Cell and Tissue Transplantation

Generating a biologic substitute tissue that resembles native articular cartilage requires living cells that are capable of synthesizing and maintaining their surrounding cartilaginous matrix. These living cells, or tissue containing living cells, may be directly transplanted into an articular cartilage defect. Once the cells have been implanted in the defect, they need to remain viable and to replicate and synthesize a durable matrix to be effective. Experimental and preliminary clinical work with tissue regeneration techniques has shown that both autologous committed chondrocytes and undifferentiated mesenchymal cells placed in articular cartilage defects survive and are capable of producing a new cartilagelike matrix.[61]

One method of trying to generate cartilage is autologous chondrocyte implantation, in which mature articular chondrocytes are harvested, expanded in cell culture, and then implanted into the defect. Other approaches to cartilage regeneration involve the use of different types of autologous cells that are less differentiated precursor cells with chondrogenic potential. These stem cells can be derived from skin, muscle, perichondrium, periosteum, synovium, bone marrow, epiphyseal plate, and peripheral blood sources. Under the influence of environmental conditions and growth factors, these cells can be induced to differentiate into mature chondrocytelike cells that may produce a hyalinelike cartilage.

Several methods of regeneration have been applied to articular cartilage defects. Both Grande et al[62] in 1989 and Brittberg et al[63] in 1996 demonstrated in rabbit models that by adding cultured chondrocytes under a transplanted periosteum graft (cambium layer facing the defect), an enhanced repair could be achieved, rather than generation of periosteal tissue alone. With these techniques, chondrocytes were released enzymatically and subjected to proliferative expansion in vitro. The resulting increased populations of cells were transplanted into cartilage defects and covered by a periosteal flap. The cells that filled the defects appear to produce a hyaline cartilage–like tissue. A periosteal flap with the cambium layer down was used to seal the transplanted cells in place and act as a mechanical barrier, which was considered to have a beneficial humoral or paracrine effect on the synthesis of reparative tissue (Fig. 10). Migration of chondrogenic cells directly from the periosteal cambium layer may also contribute undifferentiated cells to the repair process.

The autologous chondrocyte implantation technique preserves the subchondral bone plate, with a

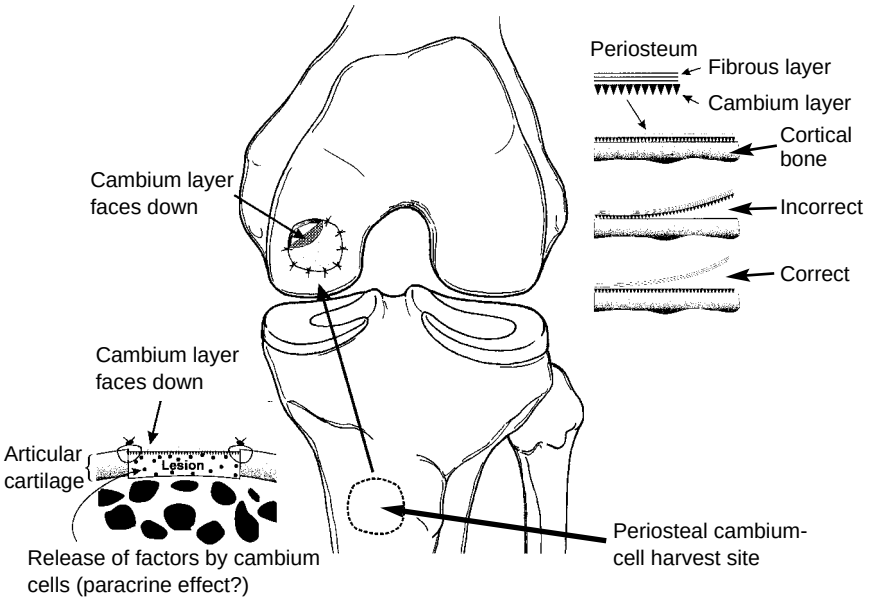

Figure 10 Autologous chondrocyte implantation technique. Articular cartilage is procured, and its chondrocytes are enzymatically released and expanded in cell culture. When a sufficient number of cells are obtained, a second operation is performed for implantation of the cultured cells. A periosteal flap with matching geometry is harvested and sutured in place with the cambium cell layer facing the defect (down). The edges of the flap are sealed with fibrin glue. **Inset,** Care must be taken when harvesting periosteum to ensure that the cambium cells remain attached to the periosteal fibrous layer.

reported high success rate.[64] In a retrospective study, Peterson et al[65] evaluated the clinical, arthroscopic, and histologic results in 101 patients who underwent autologous cultured chondrocyte transplantation. At a follow-up interval of 2 to 9 years, 92% of the patients with isolated femoral condyle lesions, 65% with chondral lesions on the patella, 67% with multiple lesions, 89% with osteochondritis dissecans lesions, and 75% with femoral condyle defects treated simultaneously with anterior cruciate ligament reconstruction had good or excellent results. Follow-up arthroscopic examinations of 53 patients showed good fill with repair tissue, good adherence to underlying bone, and hardness close to that of the adjacent tissue. Histologic analysis of 37 biopsy specimens showed an association between hyalinelike tissue and improved clinical outcomes and, conversely, between fibrous repair tissue and poor outcomes. In addition, the authors concluded that instability of the knee or abnormal weight distribution may adversely affect the results.

The current indication for implantation of autologous cultured chondrocytes is for repair of symptomatic, cartilaginous defects of the femoral condyle (medial, lateral, or trochlear) in patients who had an inadequate response to prior arthroscopic or other surgical repair. It should be used only in conjunction with debridement, placement of a periosteal flap, and rehabilitation. It is not indicated for the treatment of cartilage damage associated with osteoarthritis, and any accompanying instability or abnormal weight distribution within the joint should be corrected prior to implantation.

Osteochondral Plugs

Large untreated (empty) lesions created in weight-bearing surfaces of the medial femoral condyles in a goat model have demonstrated progressive changes in both the bone and the articular cartilage compartment over time, with an associated abortive spontaneous repair process and deleterious effects in a zone surrounding the defect (Fig. 11). Without reestablishment of a bone base that includes a subchondral plate, it is highly unlikely that a cartilaginous reparative process will progress to a functional, nondegenerative end point in larger defects.

If the defect is beyond a critical size, it appears to be difficult to achieve complete repair spontaneously. Convery et al[66] assessed the effect of defect size in the distal femur of horses and demonstrated that a large (9-mm-diameter) lesion did not heal, but that a smaller (3-mm-diameter) lesion was fully repaired by 3 months. In addition to the size of the defect, other factors that may affect a reparative process include the location of the defect in a weight-bearing area and early loading in weight-bearing areas during the initial healing process.

For full-thickness articular cartilage defects and osteochondral defects, another repair option includes the transplantation of autologous living chondrocytes with their im-

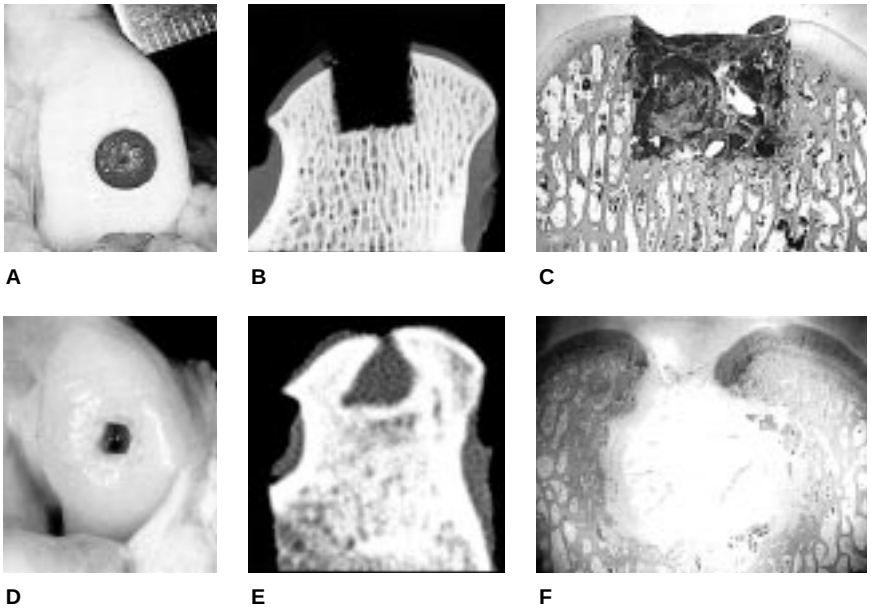

Figure 11 Appearance of a 6-mm articular cartilage lesion in the medial femoral condyle in a goat model at various time intervals after creation of the lesion. Gross appearance at time zero (immediately after lesion creation) **(A)** and 1 year postoperatively **(D)**. Articular cartilage adjacent to the defect was also affected, undergoing changes in a region called the "zone of influence," which is characterized by flattening and cartilage thinning and matrix alterations that remained abnormal throughout the study period. Coronal-section microradiographic appearance of the lesion at time zero **(B)** and computed tomographic scan obtained at 1 year **(E)** demonstrate changes in lesion geometry. Histologic sections of the lesion at 48 hours after its creation **(C)** and at 6 months show that the wall of the lesion has enlarged, and the surface articular cartilage appears to be collapsing into the defect, forming a cystlike structure **(F)**. The articular cartilage at the margins migrated over the edges of the defect, and cloned cells remained at the margins of the lesions. Furthermore, while bone has the potential to spontaneously regenerate itself, these bone defects did not regenerate or repair completely. It appears that following destruction of the subchondral plate, the reparative bone response was altered in association with the size of a defect (hematoxylin-eosin, original magnification ×10). (Adapted with permission from Jackson DW, Lalor PA, Aberman HM, Simon TM: Spontaneous repair of full-thickness defects of articular cartilage in a goat model: A preliminary study. *J Bone Joint Surg Am* 2001;83:53-64.)

mediate normal matrix intact. This substitution replacement involves the transplantation of single or multiple osteochondral grafts, commonly referred to as mosaicplasty or the Osteochondral Autograft Transplant System. This technique can be performed as an arthroscopic or limited open procedure. It involves excising all injured or unstable tissue from the articular defect and creating cylindrical holes in the base of the defect and underlying bone. These holes are filled with cylindrical plugs of healthy cartilage and bone in a mosaic fashion (Fig. 12). The osteochondral plugs are harvested from a weight-bearing area of lesser importance in the same joint. The goal is to fill the defect as completely as possible (usually 60% to 80% of the surface area). Histologic evidence demonstrates that the hyaline cartilage on the cylindrical graft has the ability to survive in its new setting and maintain its structural integrity.

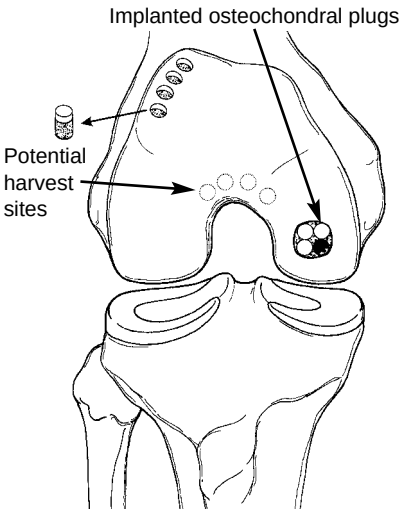

Figure 12 Osteochondral plug transplantation technique. The lesion site is prepared by debriding any loose articular cartilage, and the number and size of the plugs to be used for repair are determined. The holes to receive the plugs are drilled in the floor of the lesion. With use of specialized harvesting instrumentation, the osteochondral plugs are procured from suitable sites so as to approximate the surface geometry of the lesion site. The plugs are then implanted to the appropriate depth into the holes placed in the lesion base.

In a study on 227 patients, Hangody et al[67] reported that mosaicplasty had superior results compared with abrasion arthroplasty, microfracture, and Pridie drilling in articular lesions ranging in size from 1 to 9 cm^2. The authors concluded that the results of procedures penetrating the bone endplate deteriorate over time, with improvements ranging from 48% to 62%, while mosaicplasty results stabilize at 86% to 90% at 5 years.

Overall, the transplantation of osteochondral autografts has been shown to be an effective technique for replacing confined areas of damaged articular cartilage. The technique of fixation and the value of continuous passive motion, with altered weight bearing, are reported to be important in obtaining optimal results. Factors that can compromise the results include donor-site morbidity, the effects of joint incongruity on the opposing surface of the donor site, damage to the chondrocytes at the articular margins of the donor and recipient sites during preparation and implantation, and collapse or settling of the graft over time. In addition, articular mismatches of the surface curvature after implantation may compromise results and affect the opposing surface of the recipient site. Accurate restoration of the normal contour of the articular surface may depend on the size of the defect and the contour of the donor autograft plug, as well as appropriate depth placement of the graft.

Osteochondral Allografts

Transplantation of large allografts of bone and overlying articular cartilage is another treatment option after trauma to articular cartilage and underlying bone that involves a greater area than is suitable for autologous cylindrical plugs, as well as for a noncontained defect. Allografts have been used successfully after severe acute joint trauma and in the treatment of neoplasms involving the joint or adjacent bone. The advantages of osteochondral allografts are the potential to restore the anatomic contour of the joint, lack of morbidity related to graft harvesting, and the ability to reconstruct large defects. Better clinical results from these grafts are related to the higher percentage of chondrocytes remaining viable to maintain the extracellular matrix, healing of the junction site to the host bone, and revascularization of the graft without excessive collapse.[68] In one study,[69] the viability of chondrocytes after osteochondral allograft transplantation ranged from 69% to 99% in three grafts studied at 12, 24, and 41 months. Stored frozen irradiated osteochondral allografts were also tested as controls; no viable cells were demonstrated. Even when failure occurred, 66% of the failed grafts had viable chondrocytes.[69] However, not all studies have shown this degree of chondrocyte survival.

The success of fresh osteochondral grafts has been reported to be 75% at 5 years, 64% at 10 years, and 63% at 14 years.[68,70] Frozen allografts appear to produce results that compare favorably with those obtained with fresh grafts when used to replace localized defects of the distal femoral articular surface. The failure rate was higher for bipolar grafts than when either the tibia or the femur alone was replaced (success rate of 25% vs 70% at 10 years).[68,70] It is also less successful for patients older than 60 years of age. Unloading osteotomies have been used to enhance the success of these allografts. The best results are in single, well-demarcated, full-thickness osteochondral defects that are 2 to 5 cm in diameter in an otherwise normal knee.[68,70] Concerns related to preservation techniques, disease transmis-

sion, tissue viability, tissue availability, and immune responses to the cells or matrix (graft-host interactions) limit the use of this technique.

Biologic and Synthetic Matrices

Recent interest and research have been directed toward finding different types of both biologic and synthetic polymers to fill osteochondral defects. They may be used to cover and cushion underlying exposed bone, reestablish a congruent articulating surface, reduce crepitation and contact of bone-on-bone surfaces, act as a pain-free surface, stabilize progression of the zone of influence on adjacent tissue, and provide physical and mechanical properties of articular cartilage. Biologic scaffolds may act as carriers for transplanted cells and/or may be vehicles for delivery of signaling substances (bioactive factors) that stimulate cells to grow into them (inductive) and on them (conductive). They have the potential to minimize the number of cells lost in the synovial fluid and allow easier delivery of the cells into a defect.

Polymers can be produced in different forms and shapes and can be modified for porosity and the number of cells they contain. They may be composites and may vary in structural characteristics (e.g., hard vs soft, permanent vs bioabsorbable). Potentially, the synthetic matrices can bridge the void of the osteochondral defect to overcome the deleterious effects seen with larger lesions and can facilitate the restoration of an articulating surface. Important points in developing matrices to replace articular cartilage are mechanical stability, bonding to the host tissue, biocompatibility, internal cohesiveness, and the three-dimensional organization within the matrix. Implants may be formed from a variety of biologic and nonbiologic materials, including treated cartilage and bone matrices, collagens with or without hyaluronan, fibrin, carbon fiber, hydroxyapatite, porous polylactic acid, polytetrafluoroethylene, polyester, and other synthetic polymers.

An example of one of these synthetic polymers for localized replacement of articular cartilage lesions is flowable in situ curable polyurethane, which is being developed by Advanced Bio-Surfaces, Inc (Minnetonka, Minn).[71] This elastomer is biocompatible and has mechanical characteristics that mimic those of articular cartilage. It allows customized restoration of some articular cartilage defects with the use of minimally invasive techniques. This biomaterial is a two-part reactive system; the reactive components are liquid at room temperature but form a solid elastomeric implant within minutes after mixing and delivery. The cured polymer is cross-linked, segmented polyurethane that exhibits high tensile strength and excellent tear and fatigue resistance under physiologic conditions. The elastic deformation of the material allows impact absorption and load distribution across the implant. Some plastic deformation also occurs, allowing improved congruency with the articulating surface. Postoperative immobilization is necessary.

Although the durability of such substances after human implantation has not been established, it is hoped that synthetic polymers used for focal articular cartilage lesions may postpone or delay the need for a total joint replacement in adult patients. Utilization of these substances has the potential to delay or avoid major surgery, reduce the need for postoperative rehabilitation, and allow rapid return to full functional status. The use of local cartilage restoration procedures should not preclude a patient with osteoarthritis from undergoing a total knee replacement in the future. Until the ideal substitute is developed, achieving pain relief, restoring function, and delaying the need for joint replacement are short-term goals directing research around the world.

Rehabilitation After Cartilage Substitution

The effects of weight bearing and movement on any new articular surfaces will vary depending on the type of procedure. Rehabilitation must include appropriate levels for maintaining the surrounding articular cartilage and muscle strength. Reducing joint loading can lead to atrophy or degeneration of normal articular cartilage. Increasing joint loading through excessive use or increased magnitude can be deleterious to articular cartilage. Joint loading influences chondrocyte function beneficially or detrimentally over a very broad range and is an important part of any repair, replacement, or regenerative process. The tolerance for temporal loading of new surfaces will vary depending on the repair process and the substitute used.

Breinan et al[72] demonstrated in animal studies that there are three phases of tissue repair with cell-based therapies: the proliferative phase, which occurs at 0 to 3 months; the transitional phase, which involves macromolecular matrix production at 3 to 6 months; and finally the ongoing remodeling phase. In an environment conducive to stimulation and maturation, mechanical overloading must be avoided through protected weight bearing and functional use of the limb without impact loading, as well as correction of any malalignment or ligamentous instabilities before or during administration of cell-based therapies. Failure to recognize overloading before mechanical integration of the repair tissue is complete may result in degradation and failure of the tissue. Simultaneous correction of any factors that produced or con-

tributed to the initial lesion, such as malalignment or ligamentous instability, is critical to the success of the procedure.

Summary

Surgical considerations when utilizing cartilage substitutes should include the cause and chronicity of the defect, the general medical and systemic history of the patient, the depth of the defect, the size of the lesion, the degree of containment, the location and number of defects, ligament integrity, meniscal integrity, alignment, and previous treatments rendered. It is important to remember that not all chondral or osteochondral lesions found at magnetic resonance imaging or arthroscopy are symptomatic, even though they may play a role in future degenerative changes. It is often difficult to establish or correlate the chondral or osteochondral defect with the presence of symptoms and disability. The natural history of incidental chondral lesions discovered at arthroscopy has not yet been clarified.

There are still great differences in opinion as to which procedures have the best potential to restore functional articular cartilage–like tissue. This new and exciting field still lacks prospective, randomized, controlled clinical trials that compare the various techniques and treatment options. Furthermore, the variety of evaluation methods utilized by researchers makes comparison of data on the results obtained with the current approaches difficult to interpret. Understanding the characteristics of the available chondral substitutes and their indications and success rates will help the orthopaedic surgeon make the treatment choices that are most suitable for patients' expectations and long-term benefits.

Future developments in the field of articular cartilage substitutes will require methodical demonstration of cost-effectiveness and added value over the more established treatment alternatives. This area has a promising future for patient care that will expand in the years ahead as new technologies and advances are integrated into new clinical applications.

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