

Articular Cartilage: Injuries and Potential for Healing

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Normal pain-free movement depends on the unique properties of the articular cartilage that forms the bearing surfaces of synovial joints (19). Damage or degeneration of this remarkable tissue decreases mobility and frequently causes pain with movement and, in the most severe instances, deformity and constant pain (20,21). Limited awareness of chondral and osteochondral injuries and difficulty in diagnosing these injuries makes it impossible to accurately determine their incidence. However, arthroscopic examinations of injured knee joints suggest that closed articular surface injuries occur frequently. One group of surgeons performed arthroscopic examinations of 85 knees with traumatic hemarthrosis but absent or negligible ligamentous instability (42). Twenty percent of these knees had chondral fractures or articular surface defects. In many patients, articular surface injuries occur in association with injuries to other tissues of the synovial joint, including menisci, ligaments, joint capsule, and synovium. In these patients, the chondral and osteochondral damage may be overlooked. Advances in methods of diagnosing articular surface injuries, including arthroscopy and magnetic resonance imaging (MRI) combined with reports of new methods of stimulating cartilage repair or regeneration, have increased interest in these problems. Clinical evaluation of patients with articular surface injuries and selecting appropriate treatment requires an under-

Impact and torsional joint loading can injure articular cartilage, causing pain, joint dysfunction and effusions, and, in some instances, progressive joint degeneration. Differences in the type of injury and the repair response distinguish three classes of articular surface injuries: 1) damage to the joint surface that leaves the articular surface intact but causes internal chondral damage and may cause subchondral bone injury, 2) mechanical disruption of the articular surface limited to articular cartilage, and 3) mechanical disruption of articular cartilage and subchondral bone. A variety of treatments has the potential to improve healing of articular surfaces, including perforation of subchondral bone, altered joint loading, periosteal and perichondrial grafts, cell transplantation, growth factors, and artificial matrices. Selection of treatment for a patient with an articular cartilage injury should be guided by an understanding of the type of injury, the potential for healing, and the effects of treatment on joint surface restoration.

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standing of the mechanisms of these injuries and their natural history. This article first discusses the mechanisms of closed articular surface injuries and then considers current understanding of the responses to these injuries, methods of promoting cartilage repair, and evaluation of cartilage healing.

MECHANISMS OF ARTICULAR CARTILAGE INJURIES

Direct blunt trauma, indirect impact loading, or torsional loading of a joint can damage articular cartilage and the calcified cartilage-subchondral bone region without disrupting the surrounding soft tissues. Examples of direct blunt trauma include striking a joint with a helmet or a similar object or falling directly on a hard surface; examples of indirect impact and torsional loading include a blow to a bone that forms the subchondral part of a joint or severe twisting of a joint that is loaded. Un-

fortunately, these injuries occur frequently in people participating in sports and are difficult to diagnose.

Understanding how articular surface injuries occur requires an appreciation of how loads and rate of loading affect articular cartilage. Slowly applied loads and suddenly applied loads differ considerably in their effects. The articular cartilage extracellular matrix consists of water and a macromolecular framework formed primarily by collagens and large aggregating proteoglycans (17,19,23). The collagens give the tissue its form and tensile strength, and the interaction of aggregating proteoglycans with water gives the tissue its stiffness to compression, resilience, and probably its durability. Loading of articular surfaces causes movement of fluid within the articular cartilage matrix that dampens and distributes loads within the cartilage and to the subchondral bone (40). When this occurs slowly, the fluid movement allows the cartilage to deform and

decreases the force applied to the matrix macromolecular framework. When it occurs too rapidly for fluid movement through the matrix and deformation of the tissue, as with sudden impact or torsional joint loading of the joint surface, the matrix macromolecular framework sustains a greater share of the stress. If the stress is great enough, it ruptures the matrix macromolecular framework, damages cells, and exceeds the ability of articular cartilage to prevent subchondral bone damage by dampening and distributing loads.

In vivo, the amount of stress transmitted to a joint surface by indirect impact or torsional loading and, therefore, the probability of articular surface injury depend to some extent on whether the applied load is expected or unexpected. Muscle contractions absorb much of the energy and stabilize joints during slow expected movements or impacts. Sudden or unexpected movements or impacts may occur too rapidly for muscle contractions to stabilize joints and decrease the stress on the articular surfaces. For this reason, sudden and unexpected movements or impacts can transmit greater stress to joint surfaces and are more likely to cause articular surface injuries.

Experimental studies show that blunt trauma can damage articular cartilage and the calcified cartilage zone-subchondral bone region while leaving the articular surface intact (26,53). Physiologic levels of joint loading do not appear to cause joint injury, but impact loading above that associated with normal activities, but less than that necessary to produce cartilage disruption, can cause alterations of the cartilage matrix (26). Experimental evidence shows that loss of proteoglycans or alteration of their organization occurs before other signs of cartilage injury following impact loading (12). The loss of proteoglycans may be due either to increased degradation of the molecules or decreased synthesis. Significant loss of matrix proteoglycans de-

creases cartilage stiffness and increases its permeability (22,40,41). These alterations may cause greater loading of the remaining macromolecular framework, including the collagen fibrils, increasing the vulnerability of the tissue to further damage from loading (22). These injuries may cause other matrix abnormalities besides loss of proteoglycans, such as distortions of the collagen fibril meshwork or disruptions of the collagen fibril proteoglycan relationships, and they may injure chondrocytes.

Currently, there is no clinically applicable method of detecting alterations in cartilage matrix composition like decreased proteoglycan concentration or increased water concentration; however, new imaging techniques may provide methods of assessing articular cartilage composition and identifying joint injuries that are not detectable by physical examination or arthroscopic inspection of the joint surface. For example, magnetic resonance imaging of joints soon after an acute impact or torsional load occasionally shows changes in subchondral bone consistent with damage to the zone of calcified cartilage and subchondral bone even when the articular surface is intact (55). The altered MRI signals in subchondral bone have been referred to as "bone bruises." Presumably, the signal changes result from marrow edema that develops following bone injury. At present, the natural history of "bone bruises," their relationship to articular cartilage injuries, and their implications for long-term joint function remain uncertain. When probing the articular surface, surgeons sometimes find regions of apparent articular surface "softening" that may result from alterations in the matrix, and devices are being developed that will allow *in vivo* measurement of articular surface stiffness. Combined with information about cartilage composition and subchondral bone injury from MRI studies, these measurements may make it possible to better define injuries to

the articular surface that do not result in visible tissue disruption.

Experimental studies have shown that acute and repetitive impact loading can cause disruption of articular cartilage (12), and clinical studies have identified articular cartilage fissures, flaps and free fragments, and changes in subchondral bone similar to those produced experimentally by single and repetitive impact loads (12). In at least some patients, acute impact loading of the articular surface or twisting movements of the joint apparently caused these injuries. In other patients, the cartilage damage may have resulted from repetitive loading.

Clinical experience suggests that there are age-related differences in the risks and patterns of articular surface injuries. High energy bone or joint trauma causes intra-articular osteochondral fractures in people of all ages, but older people and people with more osteopenic bone tend to have more severely comminuted fractures. Chondral fractures associated with participation in sports generally occur in skeletally mature people, while osteochondral fractures associated with participation in sports typically occur in skeletally immature people or young adults. This difference may result from age-related changes in the mechanical properties of the articular surface, including the uncalcified cartilage, the calcified cartilage zone, and the subchondral bone. That is, age-related alterations in the articular cartilage matrix decrease the tensile stiffness and strength of the superficial zone (14,16,20,25,37), and the calcified cartilage zone-subchondral bone region mineralizes fully following completion of skeletal growth, presumably creating a marked difference in mechanical properties between the uncalcified cartilage and the calcified cartilage-subchondral bone region. Taken together, these changes probably increase the risk of ruptures of the superficial cartilage matrix and of these ruptures extending to the calci-

Injury	Clinical Presentation	Repair Response	Potential for Healing
Damage to chondral matrix and/or cells and/or subchondral bone without visible disruption of the articular surface	No known symptoms, although subchondral bone injury may cause pain Inspection of the articular surface and current clinical imaging methods for articular cartilage cannot detect this type of injury Imaging of subchondral bone by scintigraphy or magnetic resonance imaging may show abnormalities	Synthesis of new matrix macromolecules Cell proliferation?	If the basic matrix structure remains intact and enough viable cells remain, the cells can restore the normal tissue composition If the matrix and/or cell population sustains significant damage or if the tissue sustains further damage, the lesion may progress to cartilage degeneration
Cartilage disruption (chondral fractures or ruptures)	May cause mechanical symptoms, synovitis, pain, and joint effusions	No fibrin clot formation or inflammation Synthesis of new matrix macromolecules and cell proliferation, but new tissue does not fill the cartilage defect	Depending on the location and size of the lesion and the structural integrity, stability, and alignment of the joint, the lesion may or may not progress to cartilage degeneration
Cartilage and bone disruption (osteochondral fractures)	May cause mechanical symptoms, synovitis, pain, and joint effusions	Formation of a fibrin clot, inflammation, invasion of new cells, and production of new chondral and osseous tissue	Depending on the location and size of the lesion and the structural integrity, stability, and alignment of the joint, the lesion may or may not progress

TABLE 1. Chondral and osteochondral injuries.

fied cartilage-subchondral bone region. Genetically determined abnormalities of the articular cartilage may also increase the risk of chondral ruptures from a given impact or torsional load, but the relationships between known genetic abnormalities of articular cartilage and cartilage properties have not been well-defined.

RESPONSE OF ARTICULAR CARTILAGE TO INJURY

The response of articular surfaces to injury and, therefore, the potential for healing depends to a large extent on the type of injury. Excessive impact or torsional joint loading causes three types of articular cartilage injury: 1) chondral damage without visible tissue disruption, 2) disruption of articular cartilage alone (ie., chon-

dral fractures and flaps), and 3) disruption of articular cartilage and subchondral bone (ie., osteochondral fractures) (Table 1) (23,24). Intensity and rate of loading, muscle contractions that affect the transmission of force to the articular surface, age, and genetically determined differences in articular cartilage may influence the type of articular surface injury in a given individual.

Matrix and Cell Injuries

Acute or repetitive blunt trauma, including excessive impact loading, can cause alterations in articular cartilage matrix, including a decrease in proteoglycan concentration and possibly disruptions of the collagen fibril framework (12,26). The ability of chondrocytes to sense changes in matrix composition and synthesize new

molecules makes it possible for them to repair damage to the macromolecular framework. It is not clear at what point this type of injury becomes irreversible and leads to a progressive loss of articular cartilage. Presumably, the chondrocytes can restore the matrix as long as the loss of matrix proteoglycan does not exceed what the cells can rapidly produce if the fibrillar collagen meshwork remains intact and if enough chondrocytes remain viable (22-24). When these conditions are not met, the cells cannot restore the matrix, the chondrocytes will be exposed to excessive loads, and the tissue will degenerate.

Chondral Injuries

Acute or repetitive trauma can cause focal mechanical disruption of articular cartilage, including fissures,

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chondral flaps or tears, and loss of a segment of articular cartilage (12). The lack of blood vessels and lack of cells that can repair significant tissue defects limits the response of cartilage to injury (22–24). Chondrocytes respond to tissue injury by proliferating and increasing the synthesis of matrix macromolecules near the injury, but the newly synthesized matrix and proliferating cells do not fill the tissue defect and, soon after injury, the increased proliferative and synthetic activity ceases.

Osteochondral Injuries

Unlike injuries limited to cartilage, injuries that extend into subchondral bone cause hemorrhage and fibrin clot formation and activate the inflammatory response (14,22–24). Soon after injury, blood escaping from the damaged bone blood vessels forms a hematoma that temporarily fills the injury site. Fibrin forms within the hematoma and platelets bind to fibrillar collagen. A continuous fibrin clot fills the bone defect and extends for a variable distance into the cartilage defect. Platelets within the clot release vasoactive mediators and growth factors or cytokines (small proteins that influence multiple cell functions, including migration, proliferation, differentiation, and matrix synthesis), including transforming growth factor beta and platelet-derived growth factor (14). Bone matrix also contains growth factors, including transforming growth factor beta, bone morphogenetic protein, platelet-derived growth factor, insulin-like growth factor I, insulin-like growth factor II, and possibly others. Release of these growth factors may have an important role in the repair of osteochondral defects. In particular, they probably stimulate vascular invasion and migration of undifferentiated cells into the clot and influence the proliferative and synthetic activities of the cells. Shortly after entering the tissue defect, the undifferentiated mesenchymal cells

proliferate and synthesize a new matrix. Within 2 weeks of injury, some mesenchymal cells assume the rounded form of chondrocytes and begin to synthesize a matrix that contains type II collagen and a relatively high concentration of proteoglycans. These cells produce regions of hyaline-like cartilage in the chondral and bone portions of the defect. Six to eight weeks following injury, the repair tissue within the chondral region of osteochondral defects contains many chondrocyte-like cells in a matrix consisting of type II collagen, proteoglycans, some type I collagen, and noncollagenous proteins. Unlike the cells in the chondral portion of the defect, the cells in the bone portion of the defect produce immature bone, fibrous tissue, and hyaline-like cartilage.

The chondral repair tissue typically has a composition and structure intermediate between hyaline cartilage and fibrocartilage, and it rarely, if ever, replicates the elaborate structure of normal articular cartilage (Figures 1A and B). Occasionally, the cartilage repair tissue persists unchanged or progressively remodels to form a functional joint surface, but, in most large osteochondral injuries, the chondral repair tissue begins to show evidence of depletion of matrix proteoglycans, fragmentation and fibrillation, increasing collagen content, and loss of cells with the appearance of chondrocytes within a year or less (Figure 1C). The remaining cells often assume the appearance of fibroblasts as the surrounding matrix comes to consist primarily of densely packed collagen fibrils. This fibrous tissue usually fragments and often disintegrates, leaving areas of exposed bone (Figure 1C).

The inferior mechanical properties of chondral repair tissue may be responsible for its frequent deterioration. Even repair tissue that successfully fills osteochondral defects is less stiff and more permeable than normal articular cartilage, and the orientation and organization of the colla-

gen fibrils in even the most hyaline-like cartilage repair tissue does not follow the pattern seen in normal articular cartilage (Figure 1B) (20, 22). In addition, the repair tissue cells may fail to establish the normal relationships between matrix macromolecules, in particular, the relationship between cartilage proteoglycans and the collagen fibril network. The decreased stiffness and increased permeability of repair cartilage matrix may increase loading of the macromolecular framework during joint use, resulting in progressive structural damage to the matrix collagen and proteoglycans, thereby exposing the repair chondrocytes to excessive loads and further compromising their ability to restore the matrix (22).

Clinical experience and experimental studies suggest that the success of chondral repair in osteochondral injuries may depend to some extent on the severity of the injury as measured by the volume of tissue or surface area of cartilage injured and the age of the individual. Smaller osteochondral defects that do not alter joint function heal more predictably than larger defects that may change the loading of the articular surface. Potential age-related differences in healing of chondral and osteochondral injuries have not been thoroughly investigated, but bone heals more rapidly in children than in adults, and the articular cartilage chondrocytes in skeletally immature animals show a better proliferative response to injury and a greater response to anabolic growth factors and synthesize larger proteoglycan molecules than those from mature animals (14,25,39). Furthermore, a growing synovial joint has the potential to remodel the articular surface to decrease the mechanical abnormalities created by a chondral or osteochondral defect.

FACILITATING CARTILAGE REPAIR

A better understanding of articular cartilage injuries and recognition

of the limitations of the natural repair responses have contributed to the recent interest in cartilage repair and regeneration. Advances in synovial joint imaging and arthroscopic techniques have increased understanding of the frequency and types of chondral defects and made it possible to diagnose and evaluate these lesions with greater accuracy. In particular, it has become apparent that synovial joints can develop at least three types of articular cartilage defects: age-related superficial fibrillation, cartilage degeneration due to osteoarthritis, and focal chondral and osteochondral defects (36). Superficial articular cartilage fibrillation occurs in many joints with increasing age and does not appear to cause symptoms or adversely affect joint function nor does it appear to lead to progressive loss of articular cartilage. In contrast, the joint degeneration that leads to osteoarthritis consists of a generally progressive loss of articular cartilage accompanied by attempted repair of articular cartilage, remodeling and sclerosis of subchondral bone, and, in many instances, the formation of subchondral bone cysts and marginal osteophytes (20,21). In addition to the changes in the synovial joint, diagnosis of the clinical syndrome of osteoarthritis requires the presence of symptoms and signs that may include joint pain, restriction of motion, crepitus with motion, joint effusions, and deformity. Focal articular cartilage and osteochondral defects appear to result from trauma that often leaves the majority of the articular surface intact (12). They commonly occur in adolescents and young adults and, in some of these individuals, cause joint pain, effusions, and mechanical dysfunction. The pathogenesis and natural history of these three types of chondral defects differ, and it is likely that their potential for successful repair also differs.

In the last three decades, clinical and basic scientific investigations have shown that penetration of sub-

chondral bone, altered joint loading, perichondral and periosteal transplants, chondrocyte and mesenchymal stem cell transplants, growth fac-

tors, and artificial matrices facilitate formation of cartilaginous tissue in certain types of articular surface defects (20). Other work has demon-

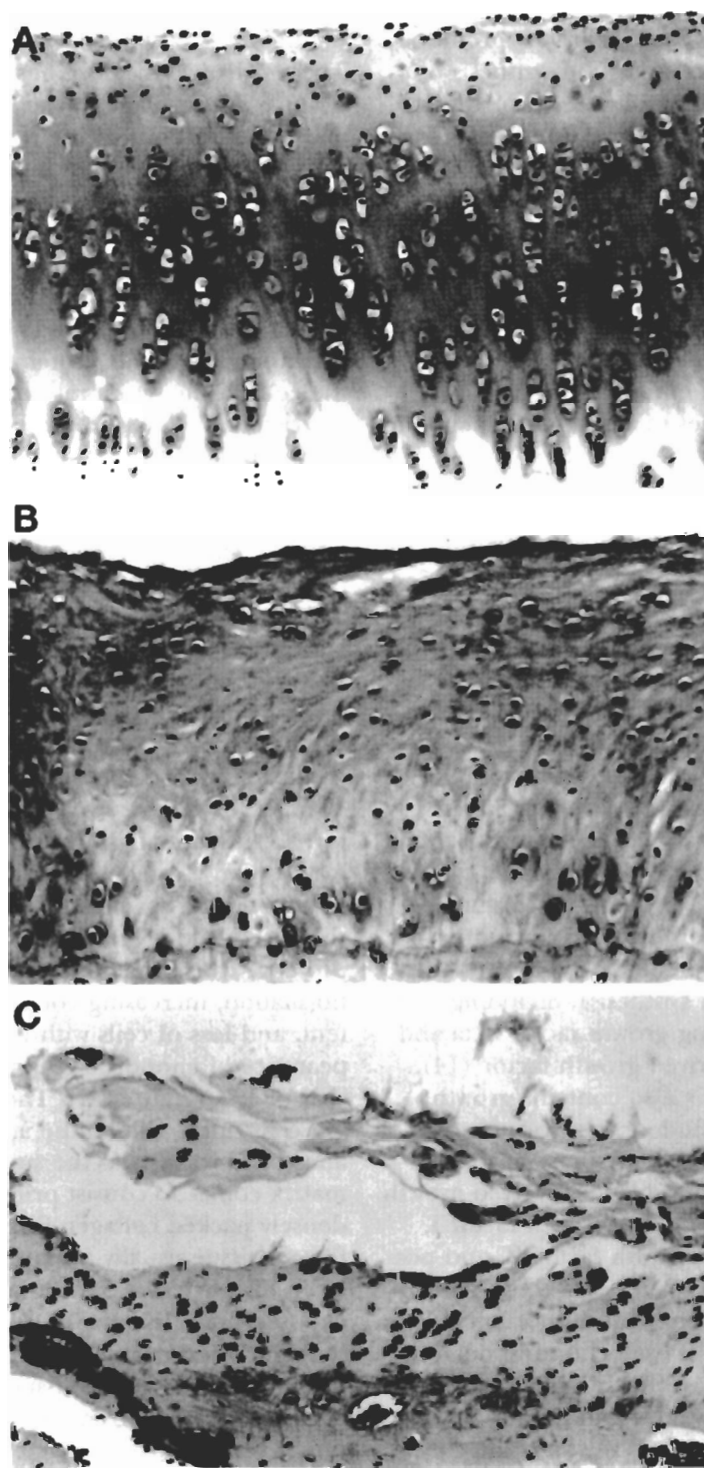


FIGURE 1. Light micrographs of rabbit articular cartilage. A) Normal articular cartilage. The articular surface is at the top. Notice the hyaline appearance of the matrix. B) Well-formed chondral repair tissue. Notice the fibrillar appearance of the matrix compared with Figure 1A. C) Fibrillated chondral repair tissue. Notice the fragmentation of the tissue. (From Buckwalter and Mow (22), reprinted with permission).

strated that mechanical loading influences the repair process in all of the tissues that form parts of the synovial joints (13,14,20) and that early controlled motion and loading can be beneficial in the treatment of joint injuries (10,14,50).

Penetration of Subchondral Bone

Surgeons have developed a variety of methods of penetrating subchondral bone to stimulate formation of a new cartilaginous surface, including drilling, abrasion of the articular surface, and making multiple small diameter defects or fractures with an awl or similar instrument. Prospective randomized controlled trials of penetrating subchondral bone to stimulate cartilage repair and decrease symptoms have not been reported, but several authors have reviewed a series of patients and found that these procedures can decrease the symptoms due to isolated articular cartilage defects and osteoarthritis of the knee (28,29,33–35,52). However, other investigators have reported less successful results (4). Examination of joint surfaces following arthroscopic abrasion has shown that, in some individuals, it results in the formation of fibrocartilaginous articular surface that varies in composition from dense fibrous tissue with little or no type II collagen to hyaline cartilage-like tissue with predominantly type II collagen (33,34). In some patients with radiographic evidence of cartilage joint space narrowing or no radiographically demonstrable joint space, the joint space increased following abrasion (33,34). Although an increase in radiographic joint space following subchondral abrasion presumably indicates formation of a new articular surface, the development of this new surface does not necessarily result in symptomatic improvement. For example, Bert and Bert and Maschka (5,6) found that 51% of 59 patients treated with abrasion arthroplasty had evidence of increased radiographic joint space 2 years after

treatment, but 31% of these individuals either had no symptomatic improvement or more severe symptoms. The lack of predictable clinical benefit from the apparent formation of cartilage repair tissue may result from variability among patients in severity of the degenerative changes, joint alignment, patterns of joint use, age, perception of pain, preoperative expectations, or other factors. It may also result from the inability of the newly formed tissue to replicate the properties of articular cartilage (22).

Decreased Articular Surface Contact Stress

Several sets of observations suggest that decreased articular surface contact stress combined with joint movement may stimulate restoration of an articular surface in osteoarthritic joints (20,22). Before the development of artificial joints, surgeons found that resection of an osteoarthritic joint surface followed by decreased loading and joint motion resulted in the formation of fibrocartilaginous tissue over the bony surfaces. When the surgeon resected the degenerated articular surfaces along with some underlying bone, the space between the bone surfaces filled with a fibrin clot and then granulation tissue. Decreased loading and motion of the resected joint facilitated formation of opposing fibrocartilaginous surfaces, immobilization, and compression promoted bony or fibrous ankylosis. Reports of the effects of releasing the muscles that act across degenerated hip joints in an attempt to decrease joint loading suggest that this procedure improved symptoms and increased the radiographic cartilage space in some patients (49). Recently, these observations concerning the effects of decreasing joint contact stress have been supported by clinical studies of the effects of joint distraction on osteoarthritic joints using external fixators (2,54).

Osteotomies realign joints, thereby altering the contact stresses on the joint surfaces. Osteotomies have not been commonly used for treatment of osteoarthritis in joints other than the hip and knee. In general, surgeons plan osteotomies to decrease loads on the most severely damaged regions of the joint surface, bring regions of the joint surface that have remaining articular cartilage into opposition with regions that lack articular cartilage, or correct joint malalignment that may contribute to symptoms and joint dysfunction. Most hip and knee osteotomies performed to treat osteoarthritis alter joint alignment in the coronal plane (varus and valgus osteotomies); however, surgeons design some hip osteotomies to change joint alignment in the sagittal plane (flexion and extension osteotomies) or alter the relationship of the joint surfaces by rotation of the femoral head relative to the acetabulum (rotational osteotomies).

The optimal planes and degrees of joint realignment for specific osteoarthritic joints have not been defined; nonetheless, clinical experience shows that osteotomies of the hip and knee can decrease symptoms and stimulate formation of a new articular surface (18). The decreased pain could result from decreasing stresses on regions of the articular surface with the most advanced cartilage degeneration decreasing intraosseous pressure or formation of a new articular surface, but the mechanisms of symptomatic improvement and formation of new articular surfaces remain poorly understood (18).

Most clinical studies have shown that in at least some patients osteotomies lead to improvement in the radiographic signs of joint degeneration, including resolution of subchondral cysts or lucencies, decreased subchondral bone density, and increased radiographic joint space (18). This latter change may result either from the altered relationship between the articular sur-

faces or the formation of a new articular surface. That is, osteotomies may alter joint alignment to separate previously opposed joint surfaces or they may rotate a cartilage-covered articular surface into opposition with a surface consisting of exposed bone, thus creating a radiographically visible cartilage space where, prior to the osteotomy, bone opposed bone. In one series of 757 intertrochanteric osteotomies performed to treat osteoarthritis of the hip, the radiographic joint space increased immediately following the procedure in approximately one-third of the patients (58). In these patients, the increased joint space presumably resulted from alterations in the relationships between the joint surfaces. In another third of the patients, the radiographic joint space increased during the next 18 months, and these individuals had better clinical results. This result suggests that in over 18 months these patients developed a new articular surface in some areas of the joint as a result of the altered loading. Reports of the treatment of degenerative disease of the knee with osteotomies also describe increased radiographic joint space accompanied by decreased subchondral bone density and, in some people, formation of a new fibrocartilaginous articular surface (18,20).

Long-term follow-up of patients treated with osteotomies for hip and knee osteoarthritis shows that the clinical results deteriorate with time (18,20). Variables that appear to adversely affect the results of knee osteotomies include advanced patient age, obesity, severe joint degeneration, joint instability, limited joint motion, operative overcorrection or undercorrection, and postoperative loss of correction. However, even patients who appear to be optimal candidates for osteotomy and who have a good initial surgical outcome tend to develop recurrent pain and evidence of advancing osteoarthritis with time.

Periosteal and Perichondrial Grafts

Periosteum and perichondrium contain cells that can form cartilage. The potential benefits of periosteal and perichondrial grafts include introduction of a new cell population along with an organic matrix, a decrease in the probability of ankylosis before a new articular surface can form, and some protection of the graft or host cells from excessive loading. Animal experiments and clinical experience show that perichondrial and periosteal grafts placed in articular cartilage defects can produce new cartilage (18,50). O'Driscoll has described the use of periosteal grafts for the treatment of isolated chondral and osteochondral defects and demonstrated that these grafts can produce a new articular surface (11,43,44). Other investigators have reported encouraging results with perichondrial grafts (27,30). However, one study suggests that increasing patient age adversely affects the results of soft tissue grafts. Seradge et al studied the results of rib perichondrial arthroplasties in 16 metacarpophalangeal joints and 20 proximal interphalangeal joints at a minimum of 3 years following surgery (51). Patient age was directly related to the results. One hundred percent of the patients in their twenties and 75% of the patients in their thirties had good results following metacarpophalangeal joint arthroplasties. Seventy-five percent of the patients in their teens and 66% of the patients in their twenties had good results following proximal interphalangeal joint arthroplasties. None of the patients older than 40 years had a good result with either type of arthroplasty. The clinical observation that perichondrial grafts produced the best results in younger patients (51) agrees with the concepts that age may adversely affect the ability of undifferentiated cells or chondrocytes to form an articular surface and that with age the population of cells that can form an articular surface declines (25).

Cell Transplantation

The limited ability of host cells to restore articular surfaces (22,23) has led investigators to seek methods of transplanting cells that can form cartilage into chondral and osteochondral defects. Experimental work has shown that both chondrocytes and undifferentiated mesenchymal cells placed in articular cartilage defects survive and produce a new cartilage matrix (18). Recently, Brittberg and Brittberg et al compared the results of treating chondral defects in rabbit patellar articular surfaces with periosteal grafts alone, carbon fiber scaffolds and periosteum, autologous chondrocytes and periosteum, and autologous chondrocytes, carbon fiber scaffolds, and periosteum (7,9). They found that the addition of autologous chondrocytes improved the histologic quality and amount of repair tissue. Other studies showed that cultured mesenchymal stem cells also can repair large osteochondral defects (56,57). In addition to these animal experiments, a group of investigators has reported using autologous chondrocyte transplants for treatment of localized cartilage defects of the femoral condyle or patella in patients (8). At 2 or more years following chondrocyte transplantation, 14 of 16 patients with condylar defects and two of seven patients with patellar defects had good or excellent clinical results. Biopsies of the defect sites showed hyaline-like cartilage in 11 of 15 femoral and one of seven patellar defects. More recently, this group of investigators has reported the results in a larger group of patients (11). They found that at more than 2 years after treatment for chondral defects of the knee, 47 of 66 patients had improved knee function. These results indicate that chondrocyte transplantation combined with a periosteal graft can promote restoration of an articular surface in humans, but more work is needed to assess the function and durability of the new tissue and de-

termine if it improves joint function and delays or prevents joint degeneration.

Growth Factors

Growth factors influence a variety of cell activities, including proliferation, migration, matrix synthesis, and differentiation. Many of these factors, including the fibroblast growth factors, insulin-like growth factors, and transforming growth factor betas, have been shown to affect chondrocyte metabolism and chondrogenesis (14,18). Bone matrix contains a variety of these molecules, including transforming growth factor betas, insulin-like growth factors, bone morphogenic proteins, platelet-derived growth factors, and others (14,15). In addition, mesenchymal cells, endothelial cells, and platelets produce many of these factors. Thus, osteochondral injuries and exposure of bone due to loss of articular cartilage may release these agents that affect the formation of cartilage repair tissue, and they probably have an important role in the formation of new articular surfaces after currently used surgical procedures, including penetration of subchondral bone.

Local treatment of chondral or osteochondral defects with growth factors has the potential to stimulate restoration of an articular surface. A recent experimental study of the treatment of partial thickness cartilage defects with enzymatic digestion of proteoglycans that inhibit adhesion of cells to articular cartilage followed by implantation of a fibrin matrix and timed release of transforming growth factor beta showed that this growth factor can stimulate cartilage repair (31,32). The cells that filled the chondral defects migrated into the defects from the synovium and formed a fibrous matrix. Despite the promise of this approach, the wide variety of growth factors, their multiple effects, the interactions among them, the possibility that the responsiveness of cells to growth fac-

tors may decline with age (25,38,48), and the limited understanding of their effects in osteoarthritic joints make it difficult to develop a simple strategy for using these agents to treat patients with osteoarthritis. However, development of growth-factor-based treatments for isolated chondral and osteochondral defects and early cartilage degenerative changes in younger people appears promising.

Artificial Matrices

Treatment of chondral defects with growth factors or cell transplants requires a method of delivering and, in most instances, at least temporarily stabilizing the growth factors or cells in the defect. For these reasons, the success of these approaches often depends on an artificial matrix. In addition, artificial matrices may allow and, in some instances, stimulate ingrowth of host cells, matrix formation, and binding of new cells and matrix to host tissue (45). Investigators have found that implants formed from a variety of biologic and non-biologic materials, including treated cartilage and bone matrices, collagens, collagens and hyaluronan, fibrin, carbon fiber, hydroxylapatite, porous polylactic acid, polytetrafluoroethylene, polyester, and other synthetic polymers, facilitate restoration of an articular surface (18,20). Lack of studies that directly compare different types of artificial matrices makes it difficult to evaluate their relative merits, but the available reports show that this approach may contribute to restoration of an articular surface (20).

Joint Loading and Motion

Achieving the best results of any method of facilitating articular cartilage repair depends on creating the optimal mechanical environment for restoration of an articular surface. The effects of joint loading and motion on articular cartilage repair remain poorly understood, but the

available evidence indicates that controlled early movement prevents cartilage degeneration following joint injury and may facilitate healing (10,14). The observations that prolonged joint immobilization and unloading injures articular cartilage, that cyclic loading increases chondrocyte synthetic activity, and that resumption of use following joint immobilization improves articular cartilage composition and mechanical properties suggest that controlled loading and motion may stimulate repair of cartilage damage limited to loss of matrix proteoglycans (10). Furthermore, in one study, active and passive motion following experimental depletion of proteoglycans stimulated restoration of matrix proteoglycans (60), but there is no evidence that joint use promotes repair of injuries that disrupt the cartilage without damaging subchondral bone. Early motion during the repair and remodeling phases of healing following osteochondral injuries can decrease or prevent adhesions and immobilization-induced deterioration of uninjured cartilage, and studies of the effects of early passive motion treatment on experimental osteochondral injuries indicate that passive motion improves the initial quality of cartilage repair tissue (50).

Despite the necessity of loading and motion for maintenance of articular cartilage and their beneficial effects following many joint injuries (19,20), premature or excessive loading and motion may delay healing or disrupt cartilage repair tissue. Following injuries associated with depletion of matrix proteoglycans, repetitive intense loading of cartilage, especially impact loading, before the chondrocytes restore the matrix proteoglycan content may cause further damage (12). Guinea pig knees subjected to chemical injury developed cartilage fibrillation and osteophytes after 3 weeks of unrestrained active joint use, and immobilization for 3 weeks prevented fibrillation and osteophyte formation (59). Running on a tread-

mill for 3 weeks following prolonged immobilization of dog knees prevented reversal of the immobilization-induced changes in cartilage proteoglycans, and early motion of knees following anterior cruciate resection appeared to increase osteophyte formation (46,47). Early loading and motion may also damage the repair tissue that forms following osteochondral injury. Examination of the effect of abrading the femoral heads of dogs showed that protection of an abraded surface from loading allowed formation of cartilage repair tissue, while areas subjected to heavy loading formed little or no repair tissue (1).

EVALUATING ARTICULAR CARTILAGE HEALING

The terms repair and regeneration are, at times, used interchangeably in discussions of approaches to restoring lost or damaged articular cartilage. To some extent, this contributes to confusion in evaluating methods of stimulating cartilage formation. Repair refers to the replacement of lost or damaged tissue with new tissue that may not duplicate the structure, composition, and function of the original tissue; regeneration refers to the formation of new tissue that duplicates the structure, composition, and function of the original tissue (14). Although repair tissue can restore an articular surface and when examined from the surface may appear nearly normal, the repair tissue does not duplicate structure, composition, and material properties of normal articular cartilage (3,22,23).

The capacity for regeneration of tissue varies among species and tissues and with age (14). Humans have the capacity to regenerate bone tissue at any age following bone fracture or, in some instances, even loss of bone tissue. Osteochondral fracture or degeneration of cartilage extending to bone can stimulate a formation of cartilaginous tissue in humans, but this tissue differs in matrix composi-

tion and mechanical properties from normal articular cartilage (Figures 1A and B) (22,23), and, thus, is not the result of articular cartilage regeneration in the strictest sense. Infants and possibly even some older children may be an exception to the lack of articular cartilage regeneration in humans (14). In some instances, they heal osteochondral injuries with tissue that cannot be distinguished from normal articular cartilage by gross inspection and imaging studies. Although regeneration of normal articular cartilage would be an optimal result of treatment of cartilage loss or damage and methods of regenerating human articular cartilage may be discovered, repair tissue can provide satisfactory function in certain circumstances.

Determining which methods have the greatest promise of restoring an articular surface depends on comparing their results. The ultimate measure of a method of articular cartilage repair or regeneration is the extent to which the method restores the long-term function of a synovial joint, that is, full painless low friction motion, distribution of loads across the joint, and durability (Table 2). The best short-term evaluation of a method of stimulating cartilage repair is the extent to which that method produces new tissue that restores joint function, structure, and an articular surface that duplicates the volume, shape, structure, composition, and mechanical properties of normal articular cartilage. Table 2 lists measures that can be used to evaluate the results of attempts to restore an articular cartilage surface.

SUMMARY AND CONCLUSIONS

Recent work has advanced understanding of articular cartilage injuries and the potential for healing of injured or degenerated joint surfaces. Traumatic articular surface injuries that cause focal tissue damage must be distinguished from age-related cartilage fibrillation that does not

progress and from progressive articular cartilage degeneration that leads to osteoarthritis. Direct blunt trauma, indirect impact loading, or torsional loading of a joint can cause three types of focal articular cartilage damage: 1) chondral damage without visible tissue disruption, 2) disruption of articular cartilage alone (ie., chondral fractures and flaps), and 3) disruption of articular cartilage and subchondral bone (ie., osteochondral fractures). Patient age and the intensity and rate of loading influence the severity and type of articular surface injury. The potential for cartilage repair differs among these three types of injury. Chondrocytes can repair chondral damage that does not include visible tissue disruption if the tissue is protected from further injury and if the matrix macromolecular framework is not severely disrupted. Chondrocytes do not repair chondral fractures and flaps in adults and, although the repair response to osteochondral fractures can produce new cartilaginous tissue, it does not restore an articular surface that duplicates the biological and mechanical properties of normal articular cartilage in skeletally mature individuals. However, the cartilaginous repair tissue can provide a functional joint surface. Penetration of subchondral bone, altered joint loading, perichondrial and periosteal grafts, cell transplants, growth factors, and artificial matrices all have the potential to facilitate formation of new cartilaginous tissue in synovial joints, but, thus far, none of these methods have been shown to predictably restore a durable articular surface in humans. The available clinical and experimental evidence indicates that future effective methods of restoring articular surfaces will begin with a detailed analysis of the structural and functional abnormalities of the involved joint. Based on this analysis, the surgeon will develop a treatment plan that potentially combines correction of mechanical abnormalities (including malalignment, instability, and

Joint symptoms and function

Pain
Range of motion
Smoothness of motion (lack of catching, locking, or crepitus)
Stability

Joint structure

Articular surface integrity, contour, and congruity
Subchondral bone contour, shape, thickness, and organization
Synovial membrane thickness and cellularity (synovitis/effusion)
Osteophytes
Alignment

Chondral repair tissue structure

Volume (thickness)
Integrity (presence or absence of fibrillation or fissures)
Binding to adjacent normal tissue
Matrix zonal organization
Cellularity (cell density)
Cell morphology (chondrocytic vs. fibroblastic)

Chondral repair tissue matrix composition

Type II collagen concentration
Type I collagen concentration
Water concentration
Aggrecan concentration, degree of aggregation, aggrecan size, and composition
Dermatan sulfate proteoglycan concentration
Noncollagenous protein concentrations (fibronectin, tenascin)

Repair tissue mechanical properties

Stiffness
Permeability
Strength
Durability

TABLE 2. Evaluating cartilage healing.

intra-articular causes of mechanical dysfunction), debridement that may or may not include limited penetration of subchondral bone, and applications of growth factors or implants that may consist of a synthetic matrix that incorporates cells or growth factors or transplants followed by a post-operative course of controlled loading and motion.

RESEARCH/CLINICAL QUESTIONS

Many important questions concerning articular cartilage injury and repair remain unanswered. Three of the most important questions in the treatment of patients with articular cartilage damage due to sports injuries are as follows: 1) What is the nat-

ural history of injuries limited to articular cartilage? 2) What is the best method of facilitating restoration of the articular surface in a patient with a localized osteochondral defect? and 3) What is the optimal regimen of joint loading and motion following an articular surface injury? JOSPT

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