CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 427S, pp. S69–S77

The Mechanobiology of Articular Cartilage Development and Degeneration

Dennis R. Carter, PhD; Gary S. Beaupré, PhD; Marcy Wong, PhD; R. Lane Smith, PhD; Tom P. Andriacchi, PhD; and David J. Schurman, PhD

The development, maintenance, and destruction of cartilage are regulated by mechanical factors throughout life. Mechanical cues in the cartilage fetal endoskeleton influence the expression of genes that guide the processes of growth, vascular invasion, and ossification. Intermittent fluid pressure maintains the cartilage phenotype whereas mild tension (or shear) promotes growth and ossification. The articular cartilage thickness is determined by the position at which the subchondral growth front stabilizes. In mature joints, cartilage is thickest and healthiest where the contact pressure and cartilage fluid pressure are greatest. The depth-dependent histomorphology reflects the local fluid pressure, tensile strain, and fluid exudation. Osteoarthritis represents the final demise and loss of cartilage in the skeletal elements. The initiation and progression of osteoarthritis can follow many pathways and can be promoted by mechanical factors including: (1) reduced loading, which activates the subchondral growth front by reducing fluid pressure; (2) blunt impact, causing microdamage and activation of the subchondral growth front by local shear stress; (3) mechanical abnormalities that increase wear at the articulating surface; and (4) other mechanically related factors. Research should be directed at integrating our mechanical understanding of osteoarthritis pathogenesis and progression within the framework of cellular and molecular events throughout ontogeny.

Articular cartilage destruction is the hallmark of osteoarthritis (OA). This age-related syndrome eventually affects every individual who survives into his or her senior years, to varying degrees. Efforts to delay the onset or slow the progression of OA will benefit from understanding the fundamental nature of the interplay between mechanical and biologic factors in cartilage biology.

Cartilage in the appendicular skeleton appears in the fifth fetal week, with the chondrification of the femur. The differentiation and organization of the tissues then proceed rapidly, and the first involuntary muscle contractions are evident at approximately 7 weeks. Fetal muscle forces and associated skeletal movements are critical for the development of joints and also for guiding perichondral and endochondral ossification processes. The forces create spatial-varying and time-varying patterns of stresses (force intensities) and strains (local deformations) throughout the cartilage rudiments. These local cues influence the biology of the cells and the developing tissues.[12,13,15]

Research in the past decade has identified an increasingly large number of genes whose expression is influenced by the local mechanical environment.[22,51] Families of genes that have been shown to have mechanosensitive members include extracellular matrix (ECM) proteins (collagens, proteoglycans, tenacins, COMP); growth proteins regulating the cell cycle (cyclins, Cdks); cytokines (IL-1, 4, 6); growth factors (TGF-βs, BMPs, Ihh), matrix metalloproteinases (MMPs); and angiogenic and antiangiogenic factors (VEGFs, CTGF, angiopoetin2, METH-1, endostatin).[22,51] The list continues to grow.

One way to study the mechanical regulation of skeletal tissues is at the molecular level. This most often is accomplished experimentally using specific loading conditions on cells or tissues to investigate molecular mechanisms. Another approach at the tissue level involves the use of computer models that calculate stress and strain distributions. These models have been extremely useful in developing a conceptual basis for understanding development, degeneration, and regeneration. These two approaches—experimental cell biology and tissue level computer modeling—must be consistent in describing the same fundamental processes.

From the Rehabilitation Research and Development Center (153), Veterans Affairs Health Care System, Palo Alto, CA.
Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.
Correspondence to: Professor Dennis R. Carter, Biomechanical Engineering Division, Mechanical Engineering Department, Stanford, CA 94305. Phone: 650-723-4784; Fax: 650-725-1587; E-mail: dcarter@stanford.edu.
DOI: 10.1097/01.blo.0000144970.05107.7e

The purpose of this paper is to present a research perspective on OA that considers the full ontogeny of diarthrodial joints. Joint development, maintenance, and degeneration are regulated by mechanical factors introduced by loading and motion. It is our premise that the syndrome of OA can occur through many different pathways, but all pathways involve the interaction of mechanical and biologic factors. Future advances in OA research will be possible if research is conducted within an ontogenetic framework that recognizes and interprets the interactions of mechanics and biology on the organ, tissue, cell, and molecular level.

Morphogenesis of Articular Cartilage

Endochondral ossification is a fundamental process by which the cartilage endoskeleton grows and ossifies during development. It involves the stages of cell proliferation, maturation (ECM production), cell hypertrophy, ECM calcification, vascular invasion, resorption of the calcified cartilage, and bone deposition. Ossification therefore is always preceded by growth. One of the most fruitful areas of modeling in cartilage mechanobiology has involved the use of linear elastic finite element models to study the role of intermittent tissue stresses and strains on endochondral growth and ossification. With linear elastic material models, the cyclic stresses can be summarized in terms of two stress invariants: 1) the hydrostatic stress, and 2) the octahedral shear stress (which causes tensile strain in some direction) (Fig 1).

From a purely mechanical perspective, cartilage tissue can tolerate hydrostatic compressive stresses extremely well because the incompressible fluid, rather that the fibrous matrix, supports the loading. However, high levels of shear or tensile strains in cartilage will cause a mechanical failure of the fibrous matrix.

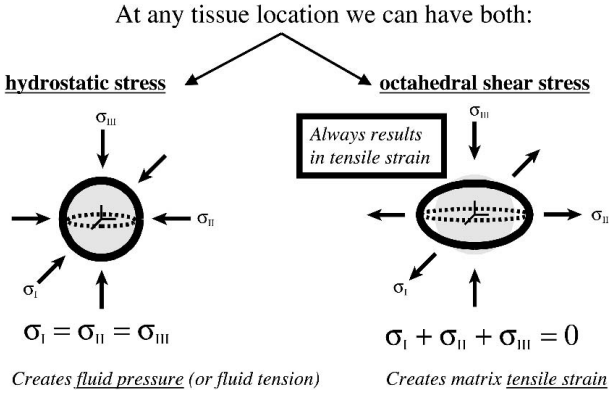

Fig 1. In a linear elastic material model, two scalar components, the hydrostatic stress and the octahedral shear stress, can represent the full stress state at any location in cartilage. Adapted with permission from Carter DR, Beaupre GS: Skeletal Function and Form: Mechanobiology of Skeletal Development, Aging, and Regeneration. Ed 1. Cambridge, England: Cambridge University Press, 2001.

From a mechanobiologic perspective, the results of numerous computational simulations support the view that under most physiologic loading conditions cartilage growth, and ossification is inhibited by the application of local intermittent hydrostatic compressive stress and accelerated by nondestructive intermittent octahedral shear stress.[10,12–15] Octahedral shear stress always causes tensile strain in some direction. Therefore, growth and ossification are accelerated by mild tensile strain, and cartilage tends to be maintained by hydrostatic compressive stress. The theoretical findings of computational studies now are gaining support from cell and tissue culture experiments. Wu et al[54] showed that tensile strain of chondrocytes increases cell proliferation, maturation, and hypertrophy while up-regulating collagen X, which is a marker for impending ossification. Intermittent hydrostatic pressure has been shown to up-regulate aggrecan and collagen II, while inhibiting proinflammatory mediators in chondrocytes.[33,45] Experiments addressing chondrometaplasia in tendons that wrap around a bony prominence indicate that local pressures up-regulate endostatin, which is an antiangiogenic factor,[39] and down-regulate VEGF.[38] The local pressures also promote the up-regulation of aggrecan and collagen II in these tendon sites.[41]

In recent in vitro tests of chondrocytes embedded in alginate gels, it was found that cyclic hydrostatic pressure decreased the mRNA levels of MMP-13 and collagen I while TIMP-1 was up-regulated.[52] Cyclic tension, however, led to an up-regulation of CTGF, MMP-13, and collagen X while down-regulating TIMP-1. Although not definitive, these results support the hypothesis that hydrostatic pressure has a chondroprotective effect and that tension (or shear) encourages growth and ossification by promoting matrix degradation and vascular invasion.[52]

The combined influences of hydrostatic pressure to maintain the mature cartilage phenotype and of shear (or tension) to accelerate endochondral ossification can be mathematically represented by the osteogenic index.[15] By applying a series of loading conditions in computer models to simulate the in vivo loading history, the distribution of osteogenic index can be calculated and displayed as contour plots. These plots then can be used to infer the distribution of ossification centers, and give some indication of the geometric advance of ossification around these centers when they form.

The basic ossification characteristics of secondary centers near a diarthrodial joint can be illustrated using the osteogenic index approach described (Fig 2). The results of the analyses predict the appearance of secondary ossification centers at the end of the rudiments on both sides

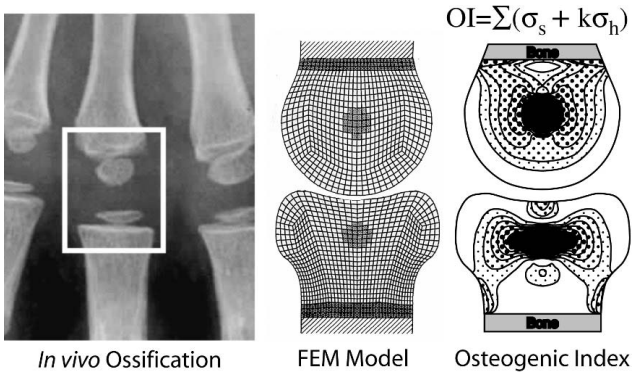

Fig 2. The location and the shape of secondary centers of ossification can be predicted from the distributions of hydrostatic and shear stresses calculated from computer models. Adapted with permission from Carter DR, Wong M: The role of mechanical loading histories in the development of diarthrodial joints. J Orthop Res 6:804–816, 1988.

of the joint.[15] In the rudiment with a concave joint surface, the secondary center is predicted to appear closer to the surface than in the rudiment with a convex surface. When the material properties of the models are changed to represent the appearance of the secondary ossification centers, subsequent analyses predict that the bone epiphysis in the convex rudiment will assume a spherical shape while the bone epiphysis in the concave rudiment will take on a flatter disclike shape. This general finding predicted by the model is evident in a wide variety of joints throughout the body.

The articular cartilage is established as the subchondral growth front approaches the articulating surface of the joint. The speed of the cartilage growth front slows as it approaches the joint surface and encounters progressively higher hydrostatic pressure. Eventually this ossification front stabilizes, thereby defining the thickness of the articular cartilage. The remaining cartilage at the bone end progressively matures into the articular cartilage that characterizes the articulating joint surface. Directly under the articular cartilage is a recognizable tidemark that demarcates a rapid transition to calcified cartilage and the underlying subchondral bone. Because of abrupt changes in tissue mechanical properties at the cartilage–bone interface, joint loading always creates shear stresses in the area of that interface. The location at which the subchondral growth front is stabilized is influenced by the relative magnitudes of the hydrostatic pressures and shear stresses in the deep cartilage zone near the tidemark.[2]

Increasing the functional loading of healthy joints by moderate exercise causes an increase in articular cartilage thickness, proteoglycan content, and mechanical stiffness of the tissue.[23,24,42] On the other hand, joint immobilization in animal models has been shown to cause an activation of the subchondral growth front that leads to cartilage vascular invasion, thinning, and loss of proteoglycan.[36,37,46] Decreased joint loading in human subjects as a result of spinal cord injury causes a decrease in cartilage thickness,[50] presumably because of the advance of the subchondral growth front.

Articular Cartilage Mechanics and Biology

The linear elastic model of articular cartilage with sweeping, time-varying loads does not capture any of the fluid flow and matrix consolidation that may occur at the articular cartilage surface. Although a consideration of flow is not necessary to understand endochondral growth and ossification inside the rudiment and young bone,[9,14] fluid flow and matrix consolidation at the joint surface is crucial in understanding joint lubrication and the mechanobiology of chondrocytes near the articular surface.[14,28,31,32,34] Poroelastic or biphasic models particularly are good for addressing this aspect of cartilage mechanobiology.

Investigators have done magnetic resonance imaging (MRI) of articular cartilage before and after various activities to assess how much fluid exudation and matrix consolidation occurs in vivo. Eckstein et al[16,17] found that young adult patellofemoral cartilage layers with a thickness of over 5 mm showed a decrease in total thickness of about 5% after severe exercise. Measurements made under various other exercise conditions prompted them to suggest that ". . . in vivo, only relatively few cycles may be necessary for the cartilage to reach a plateau-like deformation state, and that additional cycles cause no further deformation of the tissue."[16]

Although the total consolidation of articular cartilage thickness may be approximately 5% in vivo, the amount of consolidation is not constant throughout. Because the fluid primarily is exuded from the surface layer, the distribution of consolidation strains through the cartilage thickness is highly nonuniform (Fig 3). Tissue consolidation results in compressive strains of over 50% in the superficial cartilage zone, but these strains reduce to near zero in the middle and deep regions of cartilage.[51] The linearly elastic model predicts almost no compressive strain through the cartilage thickness because it has the implicit assumption of no fluid flow.

The fluid exuded in vivo gets trapped between the two articulating cartilage surfaces and maintains a high pressure level, thereby preventing the generation of high stresses and friction between the solid matrix elements of the two articulating cartilage surfaces. This pressurization has been shown in computer simulations[28,47] and has been verified experimentally.[47,48]

As articular cartilage matures under the influence of functional loading, the morphologic, biochemical, and me-

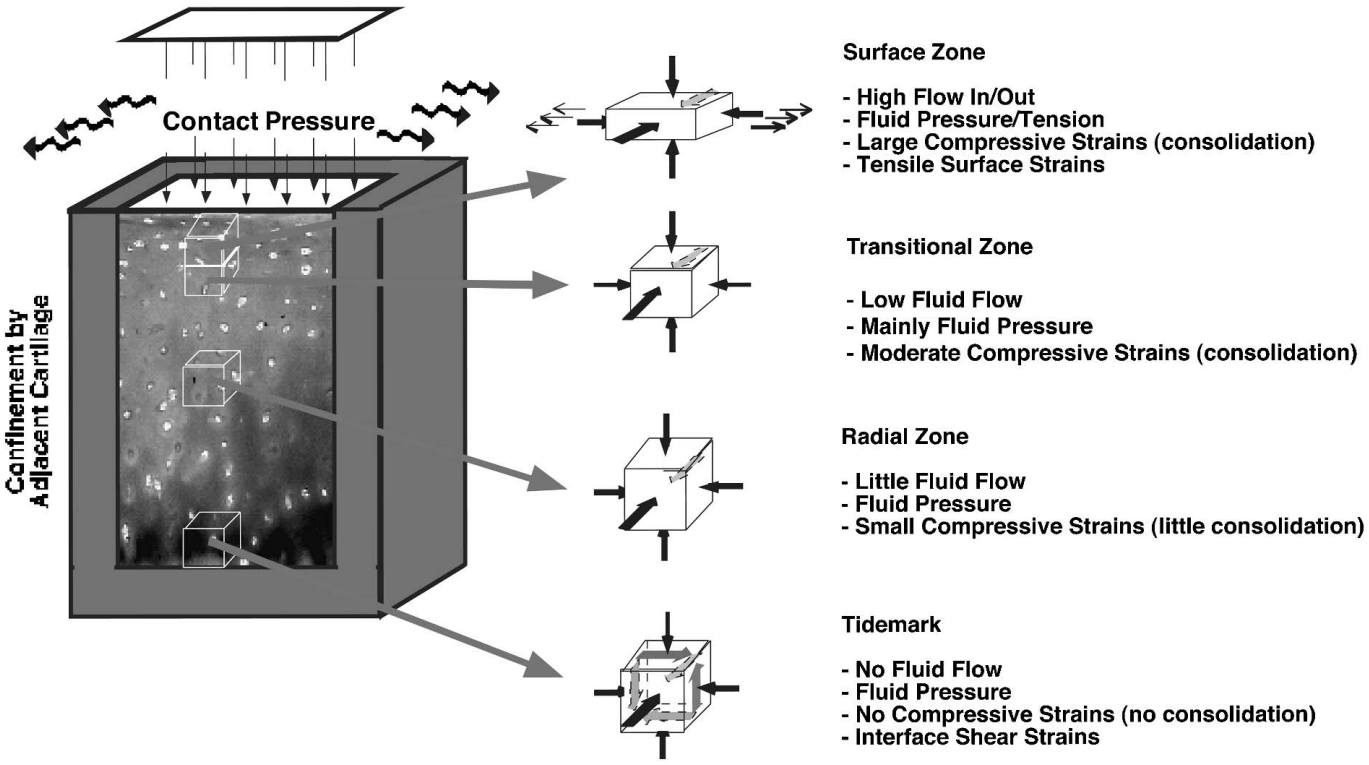

Fig 3. Schematic representation of the mechanical environment of articular cartilage under intermittent joint loading and motion is shown. Reprinted with permission from Wong M, Carter DR: Articular cartilage functional histomorphology and mechanobiology: A research perspective. Bone 33:1–13, 2003.

chanical characteristics of the tissue are established. Fetal cartilage displays flattened cell morphology along the articulating surface, but the remaining epiphysis is characterized by a homogeneous ECM in which rounded chondrocytes are dispersed. As the joint pressures increase during postnatal activity, the stratified appearance becomes clear. Chondrocytes of the middle and deep radial zones, which primarily are loaded under hydrostatic pressure and experience little strain or fluid flow, synthesize and maintain high amounts of glycosaminoglycans, uronic acid, and Type II collagen.[8,19,29,40,53] In contrast, the flattened superficial zone cells that are subjected to fluid flow and matrix consolidation in addition to hydrostatic pressure, synthesize and maintain proportionally higher amounts of collagen relative to proteoglycans, and Type I collagen may be synthesized in addition to Type II collagen.[26,35,43,49] The superficial zone cells of adult animals, but not fetal animals, synthesize a superficial zone protein, which appears to have important lubricating properties.[18,44] The variations in histomorphology lead to depth-dependent variations in mechanical properties. The tensile modulus of the superficial zone is twice as much as the deep zone, while the matrix compressive modulus is about ⅓ of that in the deep zone.[25]

These findings, and the other in vitro research described, suggests that mechanobiologic and mechanical principals for poroelastic or biphasic models of articular cartilage can be expressed as: (1) matrix consolidation, attributable to fluid exudation in the superficial zone, decreases cartilage proteoglycan content and results in a more fibrous phenotype; (2) intermittent hydrostatic fluid pressure inhibits cartilage degradation, angiogenesis, and ossification, while enhancing the extracellular matrix; (3) intermittent, mild tensile strain (or shear stress) increases cartilage cell division and ECM production, but eventually leads to apoptosis, calcified matrix degradation, vascular invasion, and ossification; and (4) excessive tensile strain (or shear stress) mechanically damages the cartilage fiber network, leading to increased wear and fibrillation, in addition to the biologically evoked degradation.

Pathogenesis of Osteoarthritis

Idiopathic Osteoarthritis and Endochondral Ossification

Articular cartilage can be considered an arrested growth front. Physiologic joint loading during development results in functional adaptation that increases the resistance of the cartilage and is beneficial to the overall health of the tissue. The areas of enriched proteoglycan content are logically the areas that are most resistant to the degenerative changes that beset a joint during OA. However, the subchondral growth front never completely is stabilized and, in fact, advances very slowly with increasing age. This advance and the associated cartilage destruction proceed faster in areas where the cartilage hydrostatic pressure is low, generally at the margins of joint surfaces.[4,5,20,21]

A systematic examination of joints that commonly develop arthritis in patients without arthritis clearly shows that the best-preserved articular cartilage is found in areas of high load bearing and contact.[4] These highly loaded areas include the superior portion of the femoral head in the hip joint (Fig 4), the tibial plateau underneath the menisci in the knee, and the humeroulnar joint in the elbow. In contrast, sites that encounter little or sporadic joint contact and pressure already show signs of fibrillation in the teenage years and by middle age are almost universally degenerated. These low load-bearing areas include the inferior portion of the femoral head below the fovea (Fig 4), the peripheral cartilage in the anterior aspect of the femoral head, the rim of the radial head of the elbow, and the lateral portion of the tibial plateau that is not covered by the meniscus of the knee.[5,6,20,21]

Although cartilage destruction is initiated in areas of little or no contact as a result of normal aging, the destruction can proceed gradually into the more heavily loaded areas. Once this occurs, the contact forces and motion at these sites can increase frictional shear stress that accelerates cartilage softening, fibrillation, and thinning as a result of wear. It also has been suggested that aging may be associated with joint laxity, which can shift the load bearing to infrequently loaded areas ill conditioned for the altered loading state, leading to mechanical damage and cartilage loss.[1] The wear process is responsible for the dramatic loss of cartilage and the appearance of eburnated bone in the areas of high joint loading that is seen in late stage OA.

As articular cartilage is destroyed, pluripotent cells from the subchondral marrow spaces are exposed. These cells normally will differentiate to form bone. In highly loaded joint areas, however, the cyclic pressure created during movement causes differentiation to be shunted down a chondrogenic pathway, producing new cartilage.[11,27] The net result is an increase in cartilage catabolism and synthesis. At the joint margins, however, endochondral ossification and bone formation proceed unabated by hydrostatic pressure, and osteophytes appear.[10]

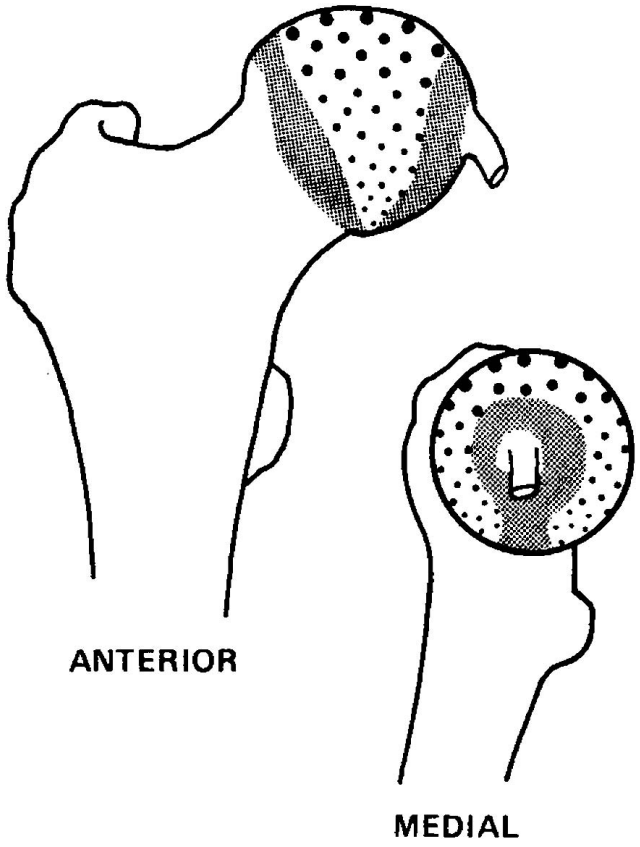

Fig 4. The areas of initial degeneration (shaded) are shown in relation to the areas of surface contact. The more heavily stippled areas indicate greater and more frequent contact pressure. Reprinted with permission from Carter DR, Rapperport DJ, Fyhrie DP, et al: Relation of coxarthrosis to stresses and morphogenesis. Acta Orthop Scand 58:611-619, 1987.

The observations that idiopathic degeneration begins in underused areas contradict two commonly held assumptions of OA: that OA is a disease that begins in old age; and that it is a disease of simple wear and tear. There are many mechanical factors that can perturb the normal mechanobiology or cause damage to the cartilage, thereby contributing to the cartilage destruction and ossification that is characteristic of all osteoarthritic joints. Fundamental mechanical perturbations that accelerate joint destruction include joint immobilization, blunt impact to joints, alterations in joint kinematics, and other mechanical-related, age-related, and genetics-related abnormalities.

Joint Immobilization

Immobilization, or other means of decreasing joint loading, effectively removes the cyclic hydrostatic pressure that is critical in maintaining the cartilage. The subchon-

dral growth front is activated and there is a vascular invasion into the cartilage, leading to a thinning, softening, and a decrease in proteoglycan content.[36,37,46] If loading is not reinstated, the growth front will advance to the joint surface, causing total cartilage destruction and bony fusion. The reduced loads also cause a reduction in subchondral bone density as a result of the bone's mechanobiologic response to reduced loading.

Blunt Impact to Joints

Joint impact loading tends to introduce damage to the bone–cartilage interface as a result of the high shear stresses that are imposed in that area. This also can activate the subchondral growth front, even though high pressures exist in the cartilage.[7,10] Cartilage degradation begins and then can be accelerated by wear and fibrillation at the articular surface. The high joint loads associated with repeated impacts will cause a concomitant increase in subchondral bone density as the bone responds to higher tissue stresses. Impact loading also can create tensile stresses in the cartilage ECM that cause weakening of the collagen interfibril connections, making the matrix more susceptible to fibrillation and wear.[30]

Alterations in Joint Kinematics

The mature cartilage has a location-dependent histomorphology that is developed in response to its specific loading history. Andriacchi et al[1] observed that ligament injury

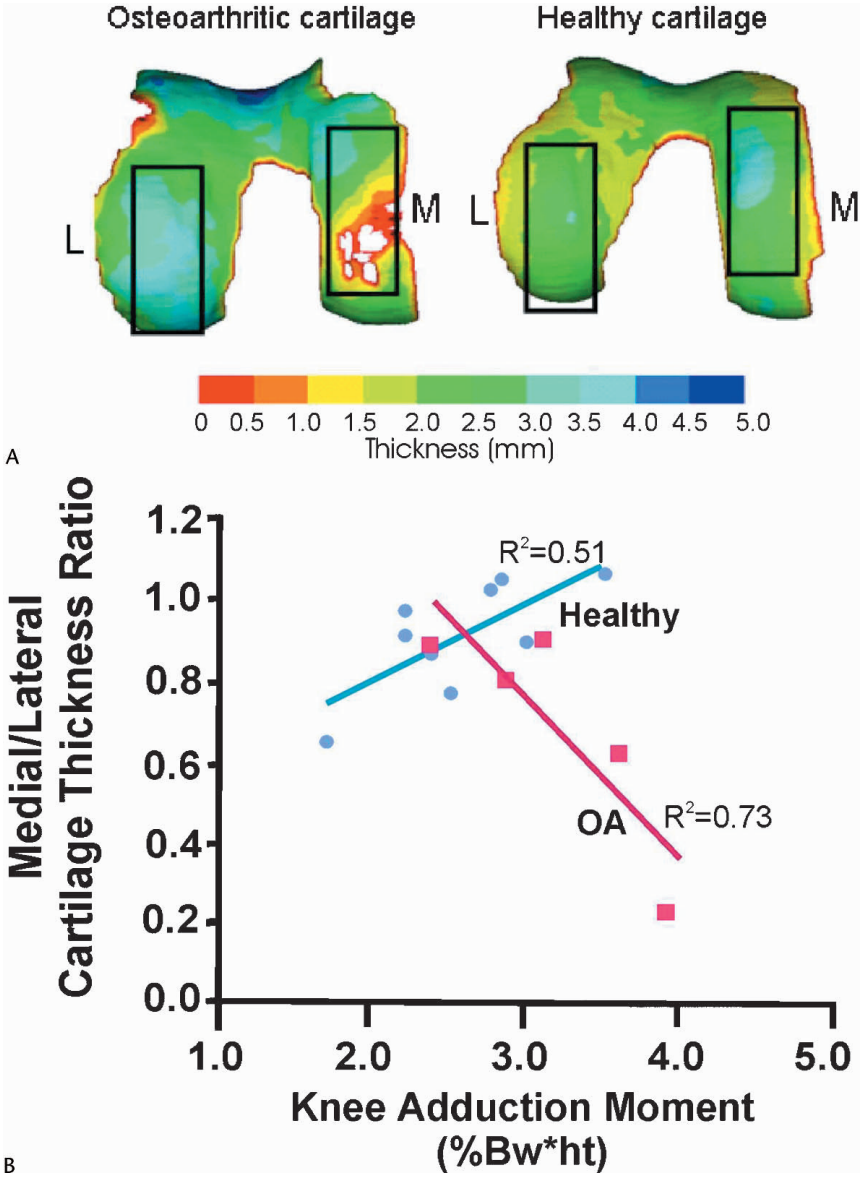

Fig 5A–B. Femoral cartilage thickness is greatest with higher loading for healthy cartilage and decreases with loading for subjects with knee OA. (A) The rectangular areas shown on the color thickness map of the distal femoral condyles indicate the load bearing regions of interest. (B) The medial-to-lateral ratio of the average ROI thickness is plotted versus the adduction moment (normalized as a percentage of body weight [Bw], times height, [ht]) for healthy and osteoarthritic subjects. Increasing adduction moment will increase the compressive contact pressure on the medial condyle. Reprinted with permission from Andriacchi T, et al: A framework for understanding the in vivo pathomechanics of osteoarthritis at the knee. Ann Biomed Eng 32:447–457, 2004.

or chronic laxity changes with aging can change the position of the contact surfaces to infrequently loaded areas. They also reported that increased cartilage thickness in subjects with healthy knees correlated with increased loading during walking. In subjects with degenerative changes, however, high loading was associated with reduced cartilage thickness (Fig 5). They concluded that the initiation of the degenerative changes was not directly because of the high contact pressures, but rather was associated with alterations in joint kinematics. Shifting the normal load-bearing regions of the cartilage to infrequently loaded regions caused mechanical damage to that cartilage, resulting in an increased coefficient of friction. The progressive increase in coefficient of friction then led to rapid disease progression in the highly loaded areas.

Other Mechanical-Related, Age-Related, and Genetics-Related Abnormalities

Cartilage can be destroyed basically by two mechanisms: (1) advance of the subchondral growth front; and (2) destruction of the tissue as a result of an imbalance among mechanical damage, synthesis, and degradation. These two processes may occur in succession or simultaneously during the initiation and progression of the disease. Consequently, many clinical situations that can lead to OA have a biomechanical and/or mechanobiologic basis. Alterations of cell and ECM biology with aging or genetic factors may contribute to a shift in the balance of synthesis and degradation, resulting in a greater propensity for endochondral ossification to proceed. Biologic and genetic factors also may cause a mechanical vulnerability of the cartilage to damage and wear. Strenuous exercise can lead to the formation of cartilage lesions,[3] increasing the susceptibility to wear damage and, possibly, to catabolic processes. Osteochondral fractures dramatically disrupt the subchondral growth front, triggering its advance while simultaneously increasing surface wear as a result of surface incongruity. Congenital or acquired deformities, abnormal loading, obesity, and other situations may be clinically identifiable features that precipitate mechanically related cartilage destruction.

DISCUSSION

The perspective that is presented here is a highly simplified one that briskly runs through many statements and arguments that can be challenged. Because of the brevity of this paper, many assumptions and shortcomings of the previous research were not addressed. Areas of possible disagreement would include our premise that OA is not a specific disease but is, in fact, linked to many of the mechanobiologic processes that regulate cartilage biology and endochondral ossification throughout life. There is also some controversy regarding the appropriate use of various engineering material models of cartilage. Additional disagreements may center on the appropriate ex vivo experimental methods that have been used to study cartilage and chondrocyte biology. More generally, there are differences of interpretation regarding the results of the many theoretical, computational, biologic, and clinical studies that have been reported in the literature. More research is needed that will support, modify, supplement, and change the ideas that we have expressed.

We have attempted to lay a foundation for understanding the role of mechanics and biology in the development and destruction of articular cartilage. The "womb-to-tomb" story of cartilage presented has at least shown that one can view OA in a broad way to observe that there are many different pathways that can lead to the demise of a joint. In addition to viewing OA as an ontogenetic process, we also have tried to emphasize the richness of understanding that can be gained from viewing joint biology concurrently on the level of organs, tissues, cells, and molecules. Our understanding must be consistent throughout all of these levels of organization. Research into cellular and molecular mechanisms viewed in such a framework may lead to effective pharmaceutical approaches to prevent and treat joint destruction. Additionally, this framework may provide a rational basis for implementing specific changes in the mechanical loading of joints to influence the pathogenesis and progression of OA.

Acknowledgments

For their contribution to the past work and ideas described here, we thank Dan Rapperport, Tracy Orr, Nick Giori, Borjana Mikic, Tishya Wren, Vineet Sarin, Sheila Stevens, Elizabeth Loboa, Sandra Shefelbine, and Marc Levenston.

References

1. Andriacchi TP, Mundermann A, Smith RL, et al: A framework for understanding the in vivo pathomechanics of osteoarthritis at the knee. Ann Biomed Eng. 32:447–457, 2004.
2. Beaupre GS, Stevens SS, Carter DR: Mechanobiology in the development, maintenance, and degeneration of articular cartilage. J Rehabil Res Dev 37:145–151, 2000.
3. Brama PA, Tekoppele JM, Bank RA, et al: The influence of strenuous exercise on collagen characteristics of articular cartilage in thoroughbreds age 2 years. Equine Vet J 32:551–554, 2000.
4. Bullough P: The pathology of osteoarthritis. In Moskowitz R et al, eds. *Osteoarthritis: Diagnosis and Medical/Surgical Management*. Philadelphia, PA: WB Saunders Company; 1992:39-69.
5. Bullough P, Goodfellow J, O'Conner J: The relationship between degenerative changes and load-bearing in the human hip. J Bone Joint Surg 55B:746–758, 1973.

6. Bullough PG, Walker PS: The distribution of load through the knee joint and its possible significance to the observed patterns of articular cartilage breakdown. Bull Hosp Jt Dis 37:110–123, 1976.
7. Burr D, Radin E: Microfractures and microcracks in subchondral bone: are they relevant to osteoarthritis? Rheum Disease Clinics North Am 29:675+, 2003.
8. Buschmann MD, Maurer AM, Berger E, et al: Ruthenium hexaammine trichloride chemography for aggrecan mapping in cartilage is a sensitive indicator of matrix degradation. J Histochem Cytochem 48:81–88, 2000.
9. Carter DR, Beaupre GS: Linear elastic and poroelastic models of cartilage can produce comparable stress results: a comment on Tanck et al. (J Biomech 32:153-161, 1999) [letter]. J Biomech 32:1255-7, 1999.
10. Carter DR, Beaupre GS: Skeletal Function and Form: Mechanobiology of Skeletal Development, Aging, and Regeneration. Ed 1. Cambridge, England: Cambridge University Press, 2001.
11. Carter DR, Beaupre GS, Giori NJ, et al: Mechanobiology of skeletal regeneration. Clin Orthop 355(Suppl):S41–S45, 1998.
12. Carter DR, Orr TE, Fyhrie DP, et al: Influences of mechanical stress on prenatal and postnatal skeletal development. Clin Orthop 219:237–250, 1987.
13. Carter DR, Rapperport DJ, Fyhrie DP, et al: Relation of coxarthrosis to stresses and morphogenesis: A finite element analysis. Acta Orthop Scand 58:611–619, 1987.
14. Carter DR, Wong M: Modelling cartilage mechanobiology. Philos Trans R Soc Lond B Biol Sci 358:1461–1471, 2003.
15. Carter DR, Wong M: The role of mechanical loading histories in the development of diarthrodial joints. J Orthop Res 6:804–816, 1988.
16. Eckstein F, Lemberger B, Stammberger T, et al: Patellar cartilage deformation in vivo after static versus dynamic loading. J Biomech 33:819–825, 2000.
17. Eckstein F, Tieschky M, Faber S, et al: Functional analysis of articular cartilage deformation, recovery, and fluid flow following dynamic exercise in vivo. Anat Embryol (Berl) 200:419–424, 1999.
18. Flannery CR, Hughes CE, Schumacher BL, et al: Articular cartilage superficial zone protein (SZP) is homologous to megakaryocyte stimulating factor precursor and Is a multifunctional proteoglycan with potential growth-promoting, cytoprotective, and lubricating properties in cartilage metabolism. Biochem Biophys Res Commun 254:535–541, 1999.
19. Franzen A, Inerot S, Hejderup SO, et al: Variations in the composition of bovine hip articular cartilage with distance from the articular surface. Biochem J 195:535–543, 1981.
20. Goodfellow JW, Bullough PG: The pattern of ageing of the articular cartilage of the elbow joint. J Bone Joint Surg 49:175–181, 1967.
21. Harrison M, Schajowicz F, Trueta J: Osteoarthritis of the hip: A study of the nature and evolution of the disease. JBJS 35B:598–626, 1953.
22. Henderson JH, Carter DR: Mechanical induction in limb morphogenesis: The role of growth-generated strains and pressures. Bone 31:645–653, 2002.
23. Jurvelin J, Kiviranta I, Tammi M, et al: Effect of physical exercise on indentation stiffness of articular cartilage in the canine knee. Int J Sports Med 7:106–110, 1986.
24. Kirviranta I, Tammi M, Jurvelin J, et al: Moderate running exercise augments glycosaminoglycans and thickness of articular cartilage in the knee joint of young beagle dogs. J Orthop Res 6:188–195, 1988.
25. Krishnan R, Park S, Eckstein F, et al: Inhomogeneous cartilage properties enhance superficial interstitial fluid support and frictional properties but do not provide a homogeneous state of stress. J Biomech Eng 125:569–577, 2003.
26. Lipshitz H, Etheredge III R, Glimcher MJ: Changes in the hexosamine content and swelling ratio of articular cartilage as functions of depth from the surface. J Bone Joint Surg 58:1149–1153, 1976.
27. Loboa E, Wren TAL, Beaupre GS, Carter DR: Mechanobiology of soft skeletal tissue differentiation: A computational approach of a fiber-reinforced poroelastic model based on homogeneous and isotropic simplifications. Biomech Model Mechanobiol 2:83–96, 2003.
28. Macirowski T, Tepic S, Mann RW: Cartilage stresses in the human hip joint. J Biomech Eng 116:10–18, 1994.
29. Maroudas A, Muir H, Wingham J: The correlation of fixed negative charge with glycosaminoglycan content of human articular cartilage. Biochim Biophys Acta 177:492–500, 1969.
30. McCormack T, Mansour JM: Reduction in tensile strength of cartilage precedes surface damage under repeated compressive loading in vitro. J Biomech 31:55–61, 1998.
31. McCutchen CW: Mechanisms of animal joints: sponge-hydrostatic and weeping bearings. Nature 184:1284–1285, 1959.
32. McCutchen CW: The lubrication of joints, in The Joints and Synovial Fluid, L. Sokoloff, Editor. Academic Press: New York. p. 437-483, 1978.
33. Mizuno S, Tateishi T, Ushida T, et al: Hydrostatic fluid pressure enhances matrix synthesis and accumulation by bovine chondrocytes in three-dimensional culture. J Cell Physiol 193:319–327, 2002.
34. Mow VC, Kuei SC, Lai WM, et al: Biphasic creep and stress relaxation of articular cartilage in compression: theory and experiment. J Biomech Eng 102:73–84, 1980.
35. Muir H, Bullough P, Maroudas A: The distribution of collagen in human articular cartilage with some of its physiological implications. J Bone Joint Surg 52:554–563, 1970.
36. O'Connor KM: Unweighting ac10.1097/01.blo.0000144970.05107.7ecelerates tidemark advancement in articular cartilage at the knee joint of rats. J Bone Miner Res 12:580–589, 1997.
37. Paukkonen K, Helminen HJ, Tammi M, et al: Quantitative morphological and biochemical investigations on the effects of physical exercise and immobilization on the articular cartilage of young rabbits. Acta Biol Hung 35:293–304, 1984.
38. Petersen W, Pufe T, Kurz B, et al: Angiogenesis in fetal tendon development: spatial and temporal expression of the angiogenic peptide vascular endothelial cell growth factor. Anat Embryol (Berl) 205:263–270, 2002.
39. Pufe T, Petersen W, Kurz B, et al: Mechanical factors influence the expression of endostatin—an inhibitor of angiogenesis—in tendons. J Orthop Res 21:610–616, 2003.
40. Ratcliffe A, Fryer PR, Hardingham TE: The distribution of aggregating proteoglycans in articular cartilage: Comparison of quantitative immunoelectron microscopy with radioimmunoassay and biochemical analysis. J Histochem Cytochem 32:193–201, 1984.
41. Robbins JR, Vogel KG: Regional expression of mRNA for proteoglycans and collagen in tendon. Eur J Cell Biol 64:264–270, 1994.
42. Saamanen A-M, Tammi M, Kiviranta I, et al: Running exercise as a modulator of proteoglycan matrix in the articular cartilage of young rabbits. Int. J. Sports Med 9: 127–132. 43, 1988.
43. Sasano Y, Furusawa M, Ohtani H, et al: Chondrocytes synthesize type I collagen and accumulate the protein in the matrix during development of rat tibial articular cartilage. Anat Embryol (Berl) 194:247–252, 1996.
44. Schumacher BL, Hughes CE, Kuettner KE, et al: Immunodetection and partial cDNA sequence of the proteoglycan, superficial zone protein, synthesized by cells lining synovial joints. J Orthop Res 17:110–120, 1999.
45. Smith R, Lin J, Trindade MCD, et al: Time-dependent effects of intermittent hydrostatic pressure on articular chondrocyte type II collagen and aggrecan mRNA expression. J Rehab R&D 37:153–162, 2000.
46. Smith RL, Thomas KD, Schurman DJ, et al: Rabbit knee immobilization: bone remodeling precedes cartilage degradation. J Orthop Res 10:88–95, 1992.
47. Soltz MA, Ateshian GA: Experimental verification and theoretical prediction of cartilage interstitial fluid pressurization at an impermeable contact interface in confined compression. J Biomech 31:927–934, 1998.
48. Soltz MA, Ateshian GA: Interstitial fluid pressurization during confined compression cyclical loading of articular cartilage. Ann Biomed Eng 28:150–159, 2000.
49. Stanescu V, Maroteaux P: Reparation differente du collagene de Type I et du Type II dans la zone superficielle et dans la zone

intermediare du cartilage articulare. CR Hebd Seances Acad Sci Ser D 283:279–282, 1976.
50. Vanwanseele B, Eckstein F, Knecht H, et al: Knee cartilage of spinal cord-injured patients displays progressive thinning in the absence of normal joint loading and movement. Arthritis Rheum 46:2073–2078, 2002.
51. Wong M, Carter DR: Articular cartilage functional histomorphology and mechanobiology: A research perspective. Bone 33:1–13, 2003.
52. Wong M, Siegrist M, Goodwin K: Cyclic tension strain and cyclic hydrostatic pressure differentially regulate expression of hypertrophic markers in primary chondrocytes. Bone 33:685–693, 2003.
53. Wong M, Wuerthrich P, Eggli P, et al: Zone-specific cell biosynthetic activity in mature bovine articular cartilage: a new method using confocal microscopic stereology and quantitative autoradiography. J Orthop Res 14:424–432, 1996.
54. Wu Q, Zhang Y, Chen Q: Indian Hedgehog is and essential component of mechanotransduction complex to stimulate chondrocyte proliferation. J Biol Chem 276:35290-35296, 2001.