Osteoarthritis is not a cartilage disease

Yet more evidence that osteoarthritis is not a cartilage disease

K D Brandt, E L Radin, P A Dieppe, L van de Putte

A better insight into the realities behind osteoarthritis

In this issue of the *Annals of Rheumatic Diseases*, Tan et al[1] report the results of high-resolution magnetic resonance imaging (hrMRI) of interphalangeal joints of 20 subjects who had "clinically osteoarthritic" and painful finger joints for <1 year. The MRI observations are supported by histological and radiographic examination of dissecting room specimens of apparently non-arthritic interphalangeal joints from three elderly people, and are an extension of earlier work by the same group of investigators.[2] Their findings indicate that structural changes in the collateral ligaments of the interphalangeal joints were uniformly present even when the articular cartilage appeared normal. The authors concluded that " ... the role of ligaments as an initiating or perpetuating factor in the pathogenesis of non-traumatic knee and hip disease merits attention. The damage evident within the small joint collateral ligaments raises the possibility that this is the principal site of wear and tear in early disease."

Observations such as these emphasise that the aetiology and progression of osteoarthritis should not be thought of as being invariably attributable to a single tissue, such as articular cartilage, but as possibly due to disease in any of the tissues of the affected organ, the diarthrodial joint, including the subchondral bone, synovium, capsule, periarticular muscles, sensory nerve endings and meniscus (if present). Supporting ligaments should be added to the list.

Although reviews of osteoarthritis often contain a statement to the effect that it is not merely a disease of cartilage, the large amounts of time, money and brainpower that have been invested in attempts to develop "chondroprotective" drugs and efforts to find the best ways to image minuscule (and clinically meaningless) changes in articular cartilage and to identify biomarkers of cartilage damage in osteoarthritis are evidence that we really do not believe what we write.

At least from the medicoeconomic and socioeconomic standpoints, the problem in fact is not structural changes in the cartilage, which almost all of us will develop in time. Rather, the problem is progressive, painful osteoarthritis. Biochemists and molecular biologists examining cartilage or bone from joints affected with osteoarthritis, or investigators assaying biological fluids for molecules derived from joints affected with osteoarthritis, reflecting the breakdown or repair of these tissues, have yet to explain why some of these joints are painful and others asymptomatic.

In a study of 19 patients with knee osteoarthritis in whom biopsy was performed on the articular cartilage on the medial femoral condyle at the time of osteotomy and again 2 years later, the second biopsy results showed the formation of a new fibrocartilaginous articular surface in nine, no change from the initial biopsy results in eight and worsening histopathology in two; no correlation was noted between the histological score, change in the radiographic appearance of the joint or the postoperative varus–valgus angle and the clinical outcome.[3] The surface of the medial tibiofemoral condyle appeared irrelevant to how the patient felt.

Osteoarthritis is a mechanically induced disorder in which the consequences of abnormal joint mechanics provoke biological effects that are mediated biochemically—for example, through cytokines, matrix-degrading enzymes and toxic oxygen radicals. Osteoarthritis develops in one of the following settings or in a combination of the two: (1) the biomaterials that comprise the various connective tissues of the joint are normal, but the mechanical stresses on the joint are excessive (eg, a baseball pitcher's elbow; the shoulder in the serving arm of a tennis pro); (2) the loads placed on the joint tissues are normal but the biomaterials abnormal.

Experiments showed that when rabbits were subjected to repeated acute (50 ms, onset to peak) impulsive loading of the knee they incurred damage to articular cartilage and subchondral bone, whereas loads of similar or greater magnitude if applied more gradually (500 ms) had no detrimental effect.[4]

Rapid delivery of load does not permit sufficient time for the periarticular muscles (see later), the major shock absorbers protecting the joints, to absorb the load.[5]

Examples of osteoarthritis developing as a consequence of defective joint tissues include the heritable systemic metabolic disease, ochronosis, which leads to premature widespread osteoarthritis because the articular cartilage becomes brittle owing to the deposition of polymers of homogentisic acid.[6] Similarly, in the chondrodysplasias that are associated with point mutations in the genes coding for type II collagen, an abnormal collagen is expressed in the cartilage matrix, affecting formation of the fibrillar extracellular network of the tissue and leading to premature cartilage failure and widespread osteoarthritis.[7][8] Many additional examples could be cited. The marked differences between the osteoarthritis phenotype of disorders such as the above, in which articular cartilage throughout the body is mechanically inferior, and that of idiopathic "primary" osteoarthritis suggests further that idiopathic primary osteoarthritis does not generally arise from an underlying cartilage defect.

LIGAMENTS

Tan et al[2] suggest that abnormalities of collateral ligaments may lead to interphalangeal joint osteoarthritis. Hunter et al[9] have recently provided longitudinal radiographic evidence to support the hypothesis that instability of the trapeziometacarpal joint with radial subluxation due to ligamentous laxity, in combination with heavy usage, may lead to radiographic thumb base osteoarthritis, a condition often far more disabling than nodal osteoarthritis.

Not surprisingly, ligament damage may result in osteoarthritis of a joint rendered unstable by the resulting laxity. The medial and lateral collateral ligaments stabilise a joint against valgus and varus stress, respectively. In Hartley Dunkin guinea pigs, a strain that "spontaneously" develops osteoarthritis of the knee, in which it was initially considered that the initial abnormalities arose in the articular cartilage, MRI studies subsequently showed changes in the subchondral bone, with remodelling of subchondral trabeculae, particularly at the insertion sites of the cruciate ligaments, which preceded changes in the articular cartilage by several weeks.[10] Similarly, in the murine model of osteoarthritis described by Van der Kraan et al,[11] induced by intra-articular injection of bacterial collagenase, severe enzymatic damage to joint structures containing type I collagen (ligaments and menisci) was seen in vivo in

conjunction with articular cartilage degeneration, although the enzyme had minimal direct effect on articular cartilage, which contains type II collagen that is resistant to digestion by the bacterial enzyme.

In humans, injury to the collateral ligaments of the knee is acknowledged to be a risk factor for knee osteoarthritis.[12–14] The ligamentous laxity associated with hypermobility syndrome is another well-recognised risk factor for osteoarthritis.[15] Sharma et al[16], emphasised the importance of varus or valgus malalignment of the knee as a risk factor for the progression of knee osteoarthritis, and Schouten et al[17] found a fivefold increase in the risk of progressive knee osteoarthritis among patients who reported a history of bow legs or knock knees in childhood. The status of the collateral ligaments of the knee was not examined in detail by MRI in those patients, as it was in the study by Tan et al,[2] but it is possible to explore the role of collateral ligament damage as a risk factor for incident knee osteoarthritis in prospective studies that use MRI.

The evidence that osteoarthritis is not merely a cartilage disease is considerable. Consider the following:

Periarticular muscle

In addition to the numerous examples of osteoarthritis resulting from joint instability due to ligamentous laxity, instability as a consequence of periarticular muscle weakness may also cause osteoarthritis. It has been shown, for example, that the quadriceps muscle is important in providing anteroposterior stability to the knee.[18]

Although weakness in the quadriceps is common in patients with knee osteoarthritis, it has generally been considered to arise as a consequence of the pain that occurs with loading of the affected joint, which leads the patient to minimise load bearing, thereby leading to disuse atrophy of the muscle. However, in addition to being the consequence of painful knee osteoarthritis, quadriceps weakness may be a risk factor for incident radiographic knee osteoarthritis.[19]

The damaging effects of impulsive loading on normal articular cartilage have been mentioned earlier. In this regard, it is relevant that in addition to its function in stabilising the knee, quadriceps contraction produces a braking action that is important in decelerating the knee immediately before heel strike. Quadriceps weakness, therefore, may result in a marked heel-strike transient and an increase in impact loading of the knee joint with ambulation.[20] In normal subjects who had no force-transient profile while walking, the load rate increased fivefold after a femoral nerve block. This suggests that a force transient can be caused by failure to decelerate the lower extremity before heel strike. Among normal subjects, minor incoordination in muscle recruitment, resulting in failure to decelerate the leg, may generate rapidly applied impulsive forces as large as 65 times the body weight at heel strike.[21]

The body's active shock-absorbing mechanisms for joints are associated with the use of muscles and joint motion in ''negative work''. Although the contraction of muscles can move a joint, muscles can also act as large rubber bands. When a slightly stretched muscle is subjected to greater stretch as a result of movement of the joint, it can absorb a large amount of energy.

When we jump off a ledge or table, for example, we normally land on our toes, come down on our heels and straighten our flexed knees and hips. During this smooth action, our muscles perform negative work—that is, they absorb energy. As we dorsiflex our ankles, we stretch our gastrocnemius–soleus complex; as we straighten our knees, we stretch our quadriceps; as we straighten our hips, we stretch our hamstrings. The amount of energy absorbed by this is very large.[22] The energy produced by normal walking is sufficient to tear all the ligaments of the knee; that this does not occur routinely attests to the importance and effectiveness of this active energy absorption mechanism.

Small, unexpected loads for which we are unprepared are much more damaging to the joints than large loads that have been anticipated. Consider what happens when we come down a flight of stairs, misjudge a step and abruptly slip the next couple of steps because our muscles are not prepared to accept the load; under these circumstances, we experience a sharp jolt. To prepare the neuromuscular apparatus to handle an impact load by reflex requires approximately 75 ms. Therefore, falls of very brief duration—for example, those of about only an inch— do not afford time to bring protective muscular reflexes into play. Under such conditions, load is transmitted to the cartilage and bone. In contrast, during a fall from a greater height, sufficient time is available for activation of the appropriate reflexes, the energy of impact is absorbed by the lengthening of the muscles around the joint, and movement of the joint and the articular cartilage and bone are protected.[23] Muscle atrophy and an increase in the latent period of the reflex (see later) that may occur with peripheral neuropathy (due to ageing or other causes) will reduce the effectiveness of this shock-absorbing mechanism. Otherwise normal people with micro-incoordination (micro-klutziness) may incur damaging loads to cartilage and bone in their knees with every step they take. Although these loads are smaller in scale than the unanticipated loads described earlier, they may nevertheless be sufficient to result in cumulative joint damage.[20]

Nerve

Proprioceptive acuity diminishes with ageing and in osteoarthritis.[24] In the case of osteoarthritis, it can be reasoned that arthritic changes damage the termini of afferent neurones associated with protective muscular reflexes. However, in patients who, on clinical and radiographic grounds, were considered to have unilateral knee osteoarthritis, a reduction in proprioception has been shown bilaterally,[25] raising the possibility that the osteoarthritis was caused by, and not merely the result of, a primary neurological defect. This possibility is strengthened by recent evidence that the impairment of proprioception that is demonstrable at the knee of patients with knee osteoarthritis is present also at the elbows.[26]

Because ligaments alone cannot prevent instability if the forces generated during strenuous activity exceed the mechanical strength of the ligament,[27] coordinated muscular activity is important in protecting joints from damage. Regardless of its cause, the role of neuropathy in osteoarthritis may be mediated by instability akin to that resulting from muscle weakness or ligament damage.

Bone

More than 30 years ago, Radin et al[28] suggested that an increase in stiffness of the subchondral bone, rendering it less capable of attenuating and distributing load throughout the joint, increased stresses in the overlying articular cartilage, leading to its deterioration in osteoarthritis. Although finite element modelling has shown that even large increases in stiffness of the bone will result in only modest increases in stress on the articular cartilage,[29] this does not mitigate the importance of bone in the pathogenesis of osteoarthritis. Rather than considering that stiffer subchondral bone causes joint breakdown in osteoarthritis by increasing stresses in the articular cartilage, a view that is more consistent with the recent evidence is that the thickening of subchondral bone in osteoarthritis is due to the increased turnover and reactivation of the secondary centre of ossification that result from the underlying change in joint mechanics. Reactivation of the secondary centre of ossification is reflected in the advance of the calcified

tissues (which is apparent histologically as a duplication of the tidemark) that leads to thinning of the hyaline cartilage by replacement with bone "from below".[30] Furthermore, this process leads to progressive joint wear, because thinned articular cartilage is highly prone to further damage and loss.[31 32]

Further evidence that bony changes may precede cartilage changes in the hand joints of patients with osteoarthritis is provided by longitudinal data[33] showing that scintigraphic changes may precede radiographic changes of osteoarthritis by months or years. These findings are consistent with the interpretation that the activity of the subchondral bone may determine loss of articular cartilage and that bone microinjury, with a resulting increase in bone turnover and remodelling, may lead to subsequent anatomical changes of osteoarthritis that eventually become apparent radiographically as, for example, subchondral sclerosis, osteophytosis and joint space narrowing (JSN).

Meniscus

Although radiographic joint space width is considered to reflect the sum of the thicknesses of the articular cartilages covering the two bones within a diarthrodial joint, and reduction in the interbone distance in serial radiographs is generally interpreted as thinning of the cartilage, subluxation of the meniscus, rather than loss of hyaline articular cartilage, may account for a large proportion of tibiofemoral compartment JSN in the knee radiographs of patients with osteoarthritis.[34 35] This, obviously, can confound the interpretation of results in clinical trials on patients with knee osteoarthritis in which the rate of JSN is used to deduce the effectiveness of a putative "chondroprotective" (or disease-modifying) osteoarthritic drug (DMOAD). It could also provide an explanation for the poor correlation between changes in the concentration of a biomarker of cartilage breakdown and loss of joint space width in some studies of knee osteoarthritis.

Articular cartilage in the osteoarthritic joint: victim of its abnormal mechanical environment

In a normal joint, the chondrocytes are subjected to physiological and, at times, excessive dynamic and static compressive, tensile and shear stresses. Work over the past several years with explants of normal articular cartilage has shown that non-injurious loading (ie, loading that does not result in the loss of proteoglycans into the culture medium or damage to the collagen network) causes physical perturbations of chondrocytes that are transduced into metabolic responses associated with changes in gene expression for aggrecan, collagen, growth factors, matrix metalloproteinases and cytokines. These constitute the normal mechanobiology of the chondrocyte.[36]

As noted above, if loading is excessive, normal articular cartilage can be damaged. In vitro, a single injurious compression of articular cartilage in explant culture resulted in about a 250-fold increase in expression of the gene for matrix metalloproteinase-3, a 40-fold increase in gene expression for ADAMTS-5 and a 12-fold increase in gene expression for tissue inhibitor of matrix metalloproteinases. Changes in the amounts of specific proteins as a result of such changes in gene expression could lead to cartilage degradation.[37] Furthermore, the effects on joint cartilage of physical forces and cytokine mediators (eg, interleukin 1 or tumour necrosis factor) may be additive. When explants of cartilage that were mechanically injured were cocultured with joint capsule/synovium they released higher levels of aggrecanase-generated fragments of aggrecan and exhibited higher levels of ADAMTS-5 (aggrecanase-2) than normal cartilage or injured cartilage cultured in the absence of joint capsule/synovium.[38] This would suggest that beyond the direct effects of the injury itself on cartilage, other tissues in the injured joint may contribute to degradation of the cartilage.

Although dose–response curves that are relevant to in vivo loading conditions are not well established, this body of data suggests that the breakdown of joint cartilage in osteoarthritis that is mediated by, for example, interleukin 1 and matrix metalloproteinases, may be driven by abnormal mechanical stresses (eg due to ligament insufficiency, muscle weakness or neuropathy that interferes with protective muscular reflexes) and that the chondropathy in so-called idiopathic osteoarthritis is, therefore, not primary but secondary.

Assuming that this perspective is correct, if efforts to develop a DMOAD or biological treatment for osteoarthritis, which are almost always aimed at stimulating the osteoarthritic cartilage with growth factors or inhibiting matrix-degrading enzymes, do not concomitantly correct the mechanical disorder that is the proximate cause of the arthropathy, these treatments are unlikely to produce long-lasting benefit.

Although gross malalignment has been an exclusion criterion in some randomised placebo-controlled clinical trials of prospective DMOADs, none has taken into account stress concentrations, proprioceptive acuity, periarticular muscle weakness or the status of the menisci. The presence of such variables may help explain why autologous chondrocyte transplantation, an effective treatment for an isolated chondral defect, such as a dashboard injury, is an ineffective treatment for osteoarthritis.[39]

CONCLUSION

In considering disease-modifying treatment for osteoarthritis, it makes more sense, in our opinion, to direct attention to the correction of the underlying mechanical abnormality than to the development of pharmacological or biological agents. Even if the biological agents should show the potential in vitro, or in relatively short-term in vivo studies in animal models, to grow new cartilage or retard the breakdown of damaged cartilage, that cartilage will exist in the same unfavourable mechanical environment that affected the joint in the first place.

Because cartilage is a relatively homogeneous tissue, lacking blood vessels and infiltrating inflammatory cells, studies of this tissue do not give rise to the myriad of problems associated with those of more complex tissues. Cartilage, therefore, attracts the attention of biochemists and of cell and molecular biologists. Osteoarthritis, however, as noted above, is not a disease of cartilage. In our opinion, only when research in osteoarthritis ceases to focus so heavily on cartilage and its cells, and attention is directed instead to the failing organ and to the local biomechanics, will we make real progress in curing or preventing osteoarthritis.

Furthermore, with respect to clinically relevant osteoarthritis, given the poor correlation that exists between the severity of structural damage and the severity of symptoms in this condition,[40] it seems that the current extensive efforts to develop radiographic protocols that provide maximum sensitivity for detection of JSN[41] and to identify surrogate biomarkers of cartilage breakdown and repair[42] are misguided.

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Authors' affiliations
K D Brandt, Indiana University School of Medicine, Indianapolis, USA
E L Radin, Tufts University School of Medicine, Boston, USA
P A Dieppe, University of Bristol, Bristol, UK
L van de Putte, University of Nijmegen, Nijmegen, The Netherlands

Correspondence to: K D Brandt, Indiana University School of Medicine, 8829 Rexford Road, IN 46260, USA; kenbrandt1@comcast.net

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