# JOINT CONTACT STRESS: A REASONABLE SURROGATE FOR BIOLOGICAL PROCESSES?

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## ABSTRACT

**A joint's normal mechanical history contributes to the maintenance of articular cartilage and underlying bone. Loading facilitates the flow of nutrients into cartilage and waste products away, and additionally provides the mechanical signals essential for normal cell and tissue maintenance. Deleteriously low or high contact stresses have been presumed to result in joint deterioration, and particular aspects of the mechanical environment may facilitate repair of damaged cartilage. For decades, investigators have explored static joint contact stresses (under some more or less arbitrary condition) as a surrogate of the relevant mechanical history. Contact stresses have been estimated *in vitro* in many joints and in a number of species, although only rarely *in vivo*. Despite a number of widely varying techniques (and spatial resolutions) to measure these contact stresses, reported ranges of static peak normal stresses are relatively similar from joint to joint across species, and in the range of 0.5 to 5.0 MPa. This suggests vertebrate diarthrodial joints have evolved to achieve similar mechanical design criteria. Available evidence also suggests some disorders of cartilage deterioration are associated with somewhat higher peak pressures ranging from 1-20 MPa, but overlapping the range of normal pressures. Some evidence and considerable logic suggests static contact stresses per se do not predict cartilage responses, but rather temporal aspects of the contact stress history. Static contact stresses may therefore not be a reasonable surrogate for biomechanical studies. Rather, temporal and spatial aspects of the loading history undoubtedly induce beneficial and deleterious biological responses. Finally, since all articular cartilage experiences similar stresses, the concept of a "weight-bearing" versus a "non-weight-bearing" joint seems flawed, and should be abandoned.**


## INTRODUCTION

Clinicians have long suspected pressure affects cartilage. Heuter recognized the effects of pressure on growth cartilage of the developing joint.[59] However, the effects on mature cartilage were not well recognized until well into the twentieth century, when the role of loading on osteoarthrosis was clearly established. Ironically, the role of loading on the normal maintenance of cartilage was recognized after its potentially deleterious effects.

Lovett, in 1891 mentioned a mechanical role in osteoarthrosis primarily to suggest it was not important.[96] Pemberton and Osgood allude to the role of mechanics in osteoarthrosis to emphasize the importance of "carriage of the body," but do not explicitly mention overloading of cartilage as the critical factor.[118] Two other authors[45,75] writing about the same time suggested repeated mild trauma was causative, although neither explored or documented this concept. Substantive consideration of a mechanical role in joint degeneration primarily occurred after the mid twentieth century. We now recognize increased loading, and ostensibly contact stresses, on articular surfaces substantially affect the durability of joints and their responses to treatment.[16,24,46]

The notion that physiological loading and motion of joints are essential for normal maintenance (i.e., metabolism) paradoxically appear to arise from observations that osteoarthritis begins in areas of the joint which were least loaded[53] and that immobilization leads to alterations in cartilage metabolism[103,142] and histology[37] of articular cartilage. Harrison et al. remarked, "Our somewhat surprising findings forced us to consider that if excess of joint pressure is deleterious to hyaline cartilage the lack of pressure is an even more compelling cause of its degeneration."[53] Thus, not only overloading, but also underloading appeared related to deleterious changes. However, *in vivo* contact stresses are typically related to motion, and the importance of motion in normal maintenance of cartilage[22,41,132] and in cartilage repair[22,55,80,131,143] is now a well accepted notion.


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Because biological changes are initiated at the local tissue level (i.e., small gross, or even microscopic level), any relevant mechanical parameter relating to tissue adaptation likely needs to be independent of area or volume of tissue or at least averaged over a very small region. That is, spatial resolution of the measures becomes a critical (although obviously question-dependent) issue. For intuitive reasons, and without any explicit consideration of this latter point, most investigators quite naturally turned to joint contact stresses as a single mechanical surrogate reflecting biological behavior.[i] In earlier studies spatially averaged contact stress was a parameter that could be readily calculated if the load and surface area were known. Methods to estimate contact stresses and their spatial distributions (with varying degrees of spatial resolution) arose only in the latter part of the twentieth century.

In this report, then, I will explore what is known about contact stresses in human and animal joints. First I will briefly describe the methods to estimate contact stresses, then I will review the quantitative estimates made by those methods, and finally I will explore the limitations of contact stress as a parameter to explain or predict clinical disease. While I do not intend a comprehensive review, it is intended to be representative.

## METHODS TO ESTIMATE CONTACT STRESSES

There are a limited number of ways to estimate contact stresses: computational approaches, individual transducers, pressure sensitive films, and pressure sensitive mats. Each approach has its advantages and limitations.

### Computational Approaches

In simple form[38,68] computational approaches were perhaps not surprisingly the earliest since they required no technology, and relatively simple models and calculations.[38,100,115,116] These sorts of models typically used a single load the authors implicitly assumed represented biologically important aspects of the mechanical history (e.g., presumed peak load during single leg stance). These approaches resulted in spatially averaged stresses, not biologically critical local peaks, and while illustrating principles did not materially advance our understanding of the biologic issues. A number of groups have reported more sophisticated computational approaches,[34,48,66,67,70,90,91] each of which necessarily includes simplifications and assumptions (some explicit, others implicit). Simplifications include geometry (often two-dimensional),[18,124] spherical hip joints, frictionless surfaces, and limited loading conditions, elastic properties. Such assumptions are not inherent, however, since with enormously enhanced computational power, models may be three-dimensional,[15,48,66,71,134] or include more sophisticated treatments of material properties,[90] or multiple loading conditions.[16,60,67,70,105] Perhaps the major question of these models is that of model confirmation.[ii] Ordinarily, this means comparing model results against some independent measure such as those from experimental techniques (see below). (It is critical to recognize we do not know whether the experiments provide "true" results: those that would be occurring naturally in the course of human or animal function. Therefore, we cannot "verify" or ascertain the truth of the model except under conditions limited to those of the experiment. In effect, perhaps the strongest corroboration arises from determining that many studies obtain similar results, despite the widely varying methods used to obtain them, and despite the many computational or experimental conditions.[iii])

### Individual Transducers

Ingelmark and Blomgren[68] recognized functional loading had an "influence . . . on the morphological and pathological state of the articular cartilages" and that a spatially averaged pressure in a joint was not likely meaningful, in contrast to a local peak. They also indicated earlier attempts to estimate pressures required "a certain amount of calculation work" and the methods were "very time-consuming." Therefore, they devised (and elegantly described) a small (9 mm diam-

[i] Oreskes[112] explores the issue of how individual parameters may inadequately capture phenomena of interest owing to both theoretical and empirical uncertainties. Although contact stress seems a reasonable parameter reflecting behavior of cartilage since it teleologically seems designed to distribute load, closer examination reveals a number of problems yet to be explored.

[ii] Oreskes and her colleagues[113] have argued numerical models of complex natural systems cannot be logically "validated" (i.e., establish the soundness or legitimacy of a proposition). In a complex system there are not only recognized parameters for which we have no quantitative knowledge, but also unrecognized parameters. In this situation, many models can produce the same result, precluding validation of any given model. Rather, we can "confirm" or strengthen our propositions.

[iii] Authors are unlikely to report a model in which experimental confirmation has been attempted, but not successful. Oreskes[113] notes she was unable to find such a case, and this author has never seen a published example. While many, if not most numerical models are published without any attempt at experimental confirmation, it is likely many models with confirmation were not initially confirmed. In these cases, authors would (appropriately) modify the model until computational and experimental answers coincided. However, this does not really imply confirmation. Rather, confirmation would need to arise from a new and fully independent set of results.

eter, 1 mm thick) rubber transducer based upon electrical inductance (and contrasted to other potential approaches based upon resistive or capacitive methods used by later investigators). This device, they reported, was accurate to within 25% of the actual pressure. Importantly, Ingelmark and Blomgren realized contact stresses averaged over some large region were not likely as biologically meaningful as local peaks: "A knowledge of such pressure peaks—should they exist—would probably be of great importance for the understanding of the pathologic changes in the joints as well as for the study of the relation between the functioning of the joints and their morphologic structure." Unfortunately, Ingelmark's device was sufficiently large that true local peaks (i.e., at the levels undoubtedly important for biological responses) could not be recorded; that is, spatial resolution was problematic. Furthermore, it was a single device that would only record in a single location, which an investigator could not a priori insure would represent stresses in an entire joint.

The transducer approach was not again utilized until the mid 1970s, when Carlson et al.[27] constructed a hemiarthroplasty device for human implantation. This device partly addressed two limitations of Ingelmark's device: measurement artifacts from insertion of a device of finite thickness between the articular surfaces and multiple transducers (14) to provide more than a single measurement. Furthermore, this device could be and indeed was implanted in humans,[52,61,62,137] allowing dynamic pressure measurements in a variety of activities. However, this device was still limited to a few discrete areas, local peak pressure estimates were limited to the size of the transducer surface, recordings could be made only of cartilage-on-metal (which would likely be quite distinct from natural cartilage-on-cartilage), and the authors reported no integration of the measurements to insure the device could recover applied loads (thus confirming the measurements). Two subsequent groups[1,20,21] did, however, map contact stresses using *in vitro* experiments. Obviously, these experiments would be limited by the limited loading conditions (which might or might not "represent" critical loading conditions from a biological point of view). Joint lubrication might also differ in the *in vitro* experiments, resulting in artifactual pressure recordings, although these differences would likely be small.

**Pressure Sensitive Films**

The problem of spatial resolution was largely solved by the introduction of a pressure sensitive film (PreScale® Fuji Film Co., Ltd., Tokyo; now distributed as Pressurex®, Sensor Products In. East Hanover, NJ) in the late 1970s.[42] (Company specifications note a spatial resolution of 5 to 15 microns, theoretically fine enough to study pressures at the cell level.) In addition, the thin nature of the film (0.076 mm) would result in relatively little artifact on flat surfaces.[141] However, since the film was not very flexible, artifacts were introduced on curved surfaces, including most animal joints. Finally, the calibration procedures were tricky. Nonetheless, owing to their advantages, a number of investigators reported *in vitro* use in the 1980s.[2,17,63,64,127,133,136,138] The images were, of course, qualitative, but scanning and semi-automated computerized approaches[26] afforded quantitative analysis of experimental replications, and comparisons of conditions. In addition, Caldwell et al.[26] reported a numerical algorithm to detect and remove crinkle artifacts in curved joints (e.g., the hip). They and others[30] further used a petal-like arrangement of the film which would fit into the joint (much like the flat paper placed on a globe of the world). Thus, the refinements provided a reasonable estimate of contact pressures with better resolution than transducers. However, these images remained "snapshots" of one point in time, and were therefore limited to a single, or at best a few, experimental loading conditions, which as noted earlier might not reflect the biologically important aspects of loading history.

**Pressure Sensitive Mats**

The ability to digitally sample and store large amounts of data afforded by computers led to a later refinement came using a mat with multiple capacitive transducers (Pedar™, novel GMBH, Munich) capable of recording dynamic pressures over time.[110] That advantage is partly offset by a mat thickness (required by the mechanical and electrical components) more likely to introduce artifact, as well as a loss of spatial resolution (imparted by limitations on sampling frequency and computer storage required for multiple sensors). Typically, the spatial resolution of these devices is in the range of 1 cm.[2] (Rapid advances in processing speeds and memory, along with affordable miniaturization of transducers may obviate reduce this limitation in the foreseeable future.) Most of the applications of these devices has been for external (e.g., skin) applications,[25,43,56,57,120] although these devices have also been developed for joints.[31,141] A major disadvantage of these mats in recording joint contact stress is their thickness (now perhaps as thin as 0.5 mm). Their introduction may result in artifactual recordings, particularly in small joints with thin cartilage. These problems have partly been solved by a different technology using high-resolution, thin-film resistive sensors (F-Scan™, Tekscan, South Boston).[5,33,40,99,122] The major problem with these devices is the stiffness of the films (considerably greater

**TABLE 1**
**Spatially Averaged and Peak Contact Stresses in Normal Joints**

| Author/Year | Species | Joint | Spatially averaged contact stress (MPa) | Peak contact) stress (MPa) |
|---|---|---|---|---|
| (Pellegrini et al., 1993) | Human | Hand | | 0.4-0.9 |
| (Tencer et al., 1988) | Human | Wrist | | 3.2 |
| (Viola et al., 1998) | Human | Radioscaphoid | 1.7±0.5 | |
| (Viola et al., 1998) | Human | Radiolunate | 1.7±0.4 | |
| (Conzen and Eckstein, 2000) | Human | Shoulder | | 10 |
| (Legal and Ruder, 1977) | Human | Hip | 0.1 | |
| (Rushfeld et al., 1979) | Human | Hip | | 6.8* |
| (Brown and Ferguson, 1980) | Human | Hip | | 10 |
| (Brinckmann et al., 1981) | Human | Hip | 1.4-1.6 | 2.4-3.2 |
| (Brown and Shaw, 1983) | Human | Hip | 2.9 | 8.8 |
| (Adams and Swanson, 1985) | Human | Hip | | 4.9-9.6 |
| (Hodge et al., 1989) | Human | Hip | | 5.5* |
| (Maxian et al., 1995) | Human | Hip | <2.0 | 6-10 |
| (Tackson et al., 1997) | Human | Hip | 5.6* | |
| (Tsumura et al., 1998) | Human | Hip | | 2.5 |
| (Hak et al., 1998) | Human | Hip | | 7.5-9.0 |
| (von Eisenhart et al., 1999) | Human | Hip | | 7.7 |
| (Hipp et al., 1999) | Human | Hip | | 2.1 |
| (Ipavec et al., 1999) | Human | Hip | | 1.6-2.7 |
| (Iglic et al., 2001) | Human | Hip | | 2.2 (male)<br>2.4 (female) |
| (Fukubayashi and Kurosawa, 1980) | Human | Tibiofemoral | | 3-4 |
| (Ahmed and Burke, 1983) | Human | Tibiofemoral | | 2.75 |
| (Brown and Shaw, 1984) | Human | Tibiofemoral | 2.6 | 8.0 |
| (Brown et al., 1991) | Dog | Tibiofemoral | | 0.5-6.0 |
| (Kuroda et al., 2001) | Human | Tibiofemoral | 0.5-0.7 | |
| (Trumble et al., 2001) | Sheep | Tibiofemoral | 1.2 | |
| (Ahmed et al., 1983) | Human | Patellofemoral | | 3.44 |
| (Manouel et al., 1992) | Human | Patellofemoral | | 0.1-1.3 |
| (Clark et al., 2002) | Cat | Patellofemoral | | |
| (Wagner et al., 1992) | Human | Ankle | | >6 MPa (20-40% of contact surface) |
| (Calhoun et al., 1994) | Human | Ankle | | 3-8 |
| (Steffensmeier et al., 1996) | Human | Ankle | 5.1±1.2 | 8.9±2.2 |
| (Rosenbaum et al., 1996) | Human | Talonavicular, Calcaneocuboid | 1.1-1.4 | 1.8-2.0 |
| (Thomas et al., 2000) | Human | Subtalar | | 2.3-6.0 |
| (Cooper et al., 1997) | Human | Calcaneocuboid | | 2.3 |
| (Lakin et al., 2001) | Human | Tarsometatarsal | 0.5-5.7 | |

**The reports involve a number of differing methods and assumptions, and with widely varying loading conditions; these numbers often reflect only a representative figure from sometimes many reported in the study. Thus, one should not attempt to directly compare the results, but rather get a sense of the range of pressures. Articles marked with an asterisk (*) arise from the only *in vivo* data in the literature but reflect cartilage-on-metal, rather than cartilage-on-cartilage contact stresses.**

than that of the Pedar™ mats) making them only useful for relatively flat surfaces.[10,31,47,93] Thus, while current approaches allow reasonable recordings of large and/or relatively flat joints, they are less useful for small or substantially curved joint surfaces.

## ESTIMATES OF NORMAL CONTACT STRESSES

Astonishingly, experimental measurements of peak or spatially averaged joint contact stresses are surprisingly similar, and within an order of magnitude of each other, regardless of the species or joint, and loading method (Table 1). Such variations as are reported can

**TABLE 2**
**Peak Contact Stresses in Abnormal Hips**

| Author/Year | Normal Hips Peak contact stress (MPa) | Dysplastic Hips Peak Peak contact stress (MPa) | Dysplastic Hips After Osteotomy(MPa) | Slipped capital femoral epiphysis after osteotomy (MPa) | Malreduced acetabular fractures Peak contact stress (MPa) |
|---|---|---|---|---|---|
| (Iglic et al., 1993) | 1.2-2.7 | 3-6 | 1.2-2.0 | | |
| (Michaeli et al., 1997) | 5-8* | 1-2.5* | | | |
| (Hak et al., 1998) | 7.5-9.0 | | | | 6.0-20.5 |
| (Tsumura et al., 1998) | 2.5 | 5.3 | | | |
| (Hipp et al., 1999) | 2.1-5.0 | 2.6-6.5 | | | |
| (Zupanc et al., 2001) | | | | 1.1-4.3 | |
| (Mavcic et al., 2000) | 2.3 | 4.6 | | | |

**The reader should again note these values reflect the methods and assumptions of the study in question, and more emphasis should be placed on relative, rather than absolute values. The higher values reported by Michaeli et al. 1997, (noted by asterisk) came from pressure sensitive films in a cadaveric pelvis, while the lower values for a "dysplastic" hip came from a plastic model in which the lateral lip was resected to simulate dysplasia. (Table taken from Brand et al., 2001, with permission.)**

readily be explained by the differences in methods (including spatial resolution for peak stresses) or experimental conditions including loads. (Most authors make the argument their loads are "physiological.") Spatially averaged stresses range from 0.1 to 2.0 MPa while peak stresses range from about 2 to 10 MPa.

## ESTIMATES OF CONTACT STRESS IN ABNORMAL CONDITIONS

Any number of clinical conditions associated with early degeneration (e.g., developmental dysplasia, slipped capital femoral epiphysis, malreduced fractures) intuitively lead to increases in contact stresses. Experimentally, compared to normal joints, a variety of studies demonstrate peak static contact stresses in such conditions are increased 2-5 times (Table 2). However, these reports show considerable variation, as well as overlap with static peak contact stresses in normal conditions. If these peak static stresses reflect the entire loading history affecting deterioration and if they have been ascertained with adequate resolution (see comments below), we could logically infer cartilage does not have a large margin of safety between the stresses required for normal maintenance, and those leading to deterioration. I hasten to add, however, these are two questionable premises, even if frequently made.[iv]

## CONTACT STRESS DISTRIBUTIONS IN NORMAL JOINTS

The reader will have just seen that peak and even spatially averaged contact pressures are remarkably similar from joint to joint and even species-to-species in the limited data on the latter. The distribution of these stresses is, however, quite variable, even within a given joint and obviously dependent upon the experimental conditions including directions of loading and constraints on bones adjacent to the joint. Pereira, et al.[119] commented, "There was a high degree of scatter in the mean pressure intensity data, which precluded our attempts to quantify this parameter." It is unlikely one can draw generalizations on the limited amount of pressure distribution.[3,4,20,21,30,130] In these limited cases, the authors illustrate isometric "contour" plots with one or perhaps two regions of highest contact stress surrounded by lower levels. These plots are based upon single instances of loading, and in a moving joint with variable loads, the patterns would differ in details both qualitatively and quantitatively.[67,104] However, not surprisingly in the human acetabulum, the patterns reflect a basic horseshoe shaped region smaller than but more or less corresponding with all but the peripheral regions of the horseshoe-shaped articular surface (if imagined flattened out), although much of the joint is unloaded or minimally loaded at any one time. Several reports suggest the resultant joint loads on the acetabulum vary considerably in location and direction throughout the gait cycle,[117,145] but remain relatively more constant in location and direction on the femoral head.[11-13,35,86,87] Thus, one would expect the contact stress patterns on the proximal femoral articular surface to be more constant than those on the acetabulum, but I am unaware of any reports documenting that point.

## WHAT ASPECTS OF JOINT CONTACT AFFECT CARTILAGE MAINTENANCE AND DEGRADATION?

At the outset, I noted the mechanical history is responsible for normal maintenance of cartilage, although

[iv] The eminent French neurologist, Paul Broca, commented, "The least questioned assumptions are often the most questionable."

at some levels is deleterious to cartilage and at yet others perhaps facilitates repair. Exploration of the effects of low, normal, and high levels of mechanical history each reflect a legitimate area of exploration, but more often than not investigators have traditionally been mostly interested in what causes tissue degeneration, and only more recently what facilitates repair. Several questions immediately arise: What aspect or aspects (parameters) of the mechanical history relate to the responsiveness of cartilage cells and cartilage as a tissue? What magnitude levels of those aspects result in normal maintenance, deterioration, repair? (In other words, what mechanical history does cartilage tolerate?) Are these levels the same in all joints? Are these levels the same for all ages? To what degree can cartilage adapt to a new and unexpected mechanical history?

**What Aspects of the Mechanical History Relate to Cartilage Biology?**

Implicitly, if intuitively, contact stresses have been used as a surrogate for whatever aspect of the mechanical history stimulates chondrocytes. Quite naturally, the choice of parameters intimately depend upon the question being asked. Whatever the question, however, a single local contact stress peak or spatially averaged peak, or even pattern measured under some loading regimen presumed representative does not likely relate directly to cartilage biology. Brown and his colleagues ascertained that while *in vitro* defects in articular cartilage result in elevated contact stresses immediately around defects, those stresses did not appear excessive (e.g., rim pressures elevated on 10-30% compared to peak local stresses on an intact surface).[19] The degree of elevation was only modestly related to defect size (1, 2, 3, 4, 5, 6, and 7 mm). The explanation for this failure to elevate stresses seems obviously related to the compliant nature of the cartilage: the rims are simply pushed into the defect, thus abrogating the effects on a rim of a more rigid surface.[44,69,129] At the same time, the radially directed peak contact stress *gradient* was elevated by as much as an order of magnitude. (Again, the degree of elevation was at best modestly related to defect size, with high gradients occurring with all sizes.) Since contact stress gradients, particularly those associated with regions of high contact stresses would relate to fluid flow,[69,101] the stress gradient more than the stress per se seems a more likely surrogate candidate if experienced over time. In a related *in vivo* experiment (but *in vitro* contact stress measurements) by Brown and colleagues, 6 mm defects allowed to repair over a period of 11 months were not associated with elevations of rim contact stresses.[109] Importantly, the repair tissue was flimsy and did not contribute to load transmission (that is, contact stresses were minimal if at all detected). This suggests remaining cartilage adapts whether by structural change[44,129] or by biological change.[89] Undoubtedly, in any joint incongruity, initially elevated contact stress gradients would disappear, and would likely do so in a fairly short time (initially owing to cartilage compliance and later owing to remodeling of the cartilage and underlying subchondral bone). Thus, if contact stress gradients per se are related to repair, they would like be so related in the early stages until adaptation occurred.

While it seems obvious that tissues respond not to some static parameter, but to complex time and spatially varying loads, it is entirely unclear what aspects of the mechanical environment and history are important. Brand and Stanford[14] proposed that tissues ignored the majority of the mechanical signals they experienced, and rather responded only to select features. This may mean many submaximal loadings might have far more effects than a few maximal loadings, in which case maximal loading (and stressing) would be irrelevant. (This would not necessarily suggest, however, that some high loading environments could not lead to damage or deterioration.) Consistent with that notion, Turner[140] proposed three rules governing the adaptation of bone to its mechanical history: 1.) Bone is driven by dynamic, rather than static, loading; 2.) Only a short duration of mechanical loading is necessary to initiate an adaptive response; 3.) Bone cells accommodate to a customary mechanical loading history, making them less responsive to routine loading signals. These notions are supported by considerable experimental evidence cited in the papers. Furthermore, Robling et al.[128] reported the same "dose" of mechanical stimulus over a period of time had differing effects on bone adaptation depending upon how the mechanical history was "partitioned." Such biological effects have been long well known in radiation biology, where "dose-fractionation" is routine part of practice.[9,73,83,135,144] Furthermore, recent experimental studies document the time scale is critical for biological responses in cartilage.[28,36,123] Thus, in ascertaining biological responses, it is insufficient just to consider contact stress magnitude, but one must also consider the time frame over which individual loading cycles are applied. Presuming these notions are correct (and substantial evidence suggests they are), and they apply to all tissues, then the contact stresses we measure may not relate directly to *in vivo* cartilage responses. While both contact stresses and stress gradients reflect the local distributions of overall joint loads, until and unless we ascertain the contact stress or contact stress gradient *dose history*—or "stress profile"[114]—which relates to cartilage biology, we will undoubtedly gain limited insight.

Another important issue in ascertaining an optimal range of mechanical histories for cartilage maintenance, adaptation, or repair relates to spatial scale. If deleteriously high stress histories occur over a small area (or volume) involving a few cells, will that region die and lead to clinically significant consequences? I think this unlikely since a small region of dead cells can probably recover. However, what if the area of cell death is over 100 micrometers, or, say 1 mm?

Cartilage has limited capacity for repair.[98] In fact, all known cells have limits on their ability to replicate ("Hayflick limit").[51,58,76,92,97,108] This limited replicative capacity appears to be related to the length of a fragment (telomere) on the end of DNA chains.[6,7,32,49-51,81,92,94,102] With each replication the telomere length is reduced and when it is sufficiently short, replication cases. Cartilage cells, in particular appear to have a very limited capacity to replicate,[84,85,102] with perhaps only 25-35 doublings during the life of a cell (contrasted to perhaps 40-60 or more with other sorts of cells). Further, "replicative senescence" is preceded by a phenotypic senescence.[125] Thus, the capacity of cartilage to produce molecules essential for maintenance, may be especially limited in aged cartilage due to a larger fraction of senescent chondrocytes. If the cells in a small region (say 100 micrometers volume) of chronically overloaded cartilage replicate and/or produce extra matrix to adapt, and subsequently become prematurely senescent they will then fail to maintain their region of matrix and the local mechanical properties will change. When this happens adjacent areas will have to take up the load, thus leading to overloading and destruction in the adjacent region, creating a vicious cycle in a spatially expanding region. Huberti and Hayes[63] noted high local patellofemoral contact stresses (approximately 3-5 MPa) in the normal-appearing cartilage in knees with degeneration of the patellar cartilage elsewhere, and low stresses in the regions of clearly abnormal cartilage. It is unclear, however, whether the regions or volumes of articular cartilage that were degenerated and under low contact stress in the experiment once under high contact stress prior to degeneration, although their observations are consistent with that notion. Further, while we do not know what regions or volumes of cartilage can be irreparably damaged, quantitative information of this sort is critical to knowing the spatial resolution required for any measures of contact stress. Thus, the notion of contact stress *histories* aside, a technique with a spatial resolution of 5 mm may be entirely insensitive to the changes in contact stresses to answer a question relevant to tissue repair or deterioration.

**What Magnitude Levels of Those Aspects of Contact Stress Dose History Result in Normal Maintenance, Deterioration, Repair?**

Few *in vivo* or *ex vivo* studies address this important question. Repo and Finlay[126] demonstrated impact stresses of 25 MPa (and strain rates of 500 and 1000 per second) were sufficient to cause chondrocyte death. This level of contact stress is also close to the level required to produce patellar fracture.[54] Thus, at the high end, a single load producing 25 MPa will likely result in either fracture or chondrocyte cell death. However, it is important to recognize that cartilage normally experiences peak contact stresses 1 to 2 orders of magnitude below this level (Table 1). Since a single accidental impact load engendering stresses below these levels is unlikely to result in local peak contact stresses and stress patterns similar to normal, we could argue a single contact stress load is unlikely to relate to subsequent cell behavior. Recognizing stress history, not single loading is critical, Brown and colleagues[48,105] estimated the contact stress histories for 83 patients with developmental dysplasia of the hip followed for an average of 29 years, and demonstrated the propensity for degeneration related to the cumulative contact stress "overdose." That overdose was at a level of 10 MPa-years, where the contact stress reflected a spatial mean. (Note this figure arises not from local peaks, but spatial averages that would generally be an order of magnitude lower.) Importantly, "single-time snapshot pressures" correlated only weakly (r=0.39) with long-term outcome. This again suggests, static contact stresses are not likely a good surrogate for biological behavior. I am unaware of any other attempts to address this question. However, these studies do suggest possible bounds on cartilage tolerance.

**Are These Levels the Same in All Joints?**

The differences in propensity for osteoarthrosis between various joints is well known epidemiologically.[39,65,82] Less well understood are the mechanical[78,139] and biological differences between the cartilage in differing joints.[29,77,139] Thus, it appears the adaptation to cartilage in each joint is unique, and it is possible the levels of dose history required for normal maintenance and damage differ. However, this argument is speculative based upon inferential evidence.

**Are These Levels the Same for All Ages?**

Age-related changes in the biological[23,77,82,106,107,121] as well as mechanical[8,78,79,111] behavior of joints are well known. As with the question of differing joints, however, whether and to what degree the mechanical dose

histories relate to tissue biology are unknown. However, investigators exploring the relationship between mechanical histories and cartilage responses should be aware that age is likely an important factor.

### To What Degree Can Cartilage Adapt to a New and Unexpected Mechanical History?

Despite the important nature of this question, evidence again remains sketchy. There is little question cartilage can adapt[74,95] or repair to at least a limited degree[72,88] in response to a new mechanical history. However, virtually nothing quantitative is known about the optimal contact stress histories required for repair.

## COMMENT

The loading history of a joint, or a region of a joint is critical to normal maintenance of articular cartilage. Investigators have long assumed contact stress a suitable mechanical parameter relating to cartilage biology. However, for a variety of reasons, that assumption is not likely a reasonable one for answering most questions relating to cartilage maintenance, adaptation, repair, and deterioration. First, a single, or even a few, contact stress measurements under very well defined (ostensibly needed for reproducibility) and restricted loading conditions may not adequately represent all those experienced by a joint. Second, all biological responses occur because of a loading ("dose") history, and given evidence cells and tissues respond to a minority of their mechanical history, we do not know which aspects of even a contact stress history result in subsequent responses. Third, the region of cells or tissues which if irreparably damaged will ultimately lead to failure of joint repair and degeneration is not known. Without some knowledge of tissue tolerance, we cannot speculate the required resolution of contact stress patterns, and rather must presume fine resolution is required. Fourth, the levels of the contact stress history which result in normal maintenance or degeneration are not known, but limited evidence suggests a spatially averaged (not peak local) joint contact stress "dose" of 10 MPa-years appears to be deleterious.

The basis for the critical nature of intermittent joint loading in maintaining normal articular cartilage is sound, and experimental studies consistently support the concept. Intermittent loading results in flow of nutrients into and waste products out of cartilage, and in addition provides the mechanical signals essential for normal cell and tissue maintenance. On the other hand, deleteriously low or high contact stresses result in joint deterioration. Particular aspects of the environment may facilitate repair of damaged cartilage. However, I am unaware of any such studies that attempted to quantify the mechanical history, and in particular the contact stress history in their protocols. It would seem, however, based upon other evidence, motion alone in the absence of adequate contact stress would not suffice for either maintenance or repair of cartilage.

Contact stresses have been estimated in many joints, and in a number of species, although rarely *in vivo*. Despite a number of widely varying techniques to measure these contact stresses, the ranges of peak normal stresses are relatively similar from joint to joint across species, and in the range of 0.5 to 5.0 MPa. This suggests diarthrodial joints have evolved with similar tissues (cartilage, underlying bone, ligaments, capsule) to achieve similar mechanical design criteria, and that the articular cartilage in particular normally experiences a narrow range of contact stresses. Disorders resulting in elevated static peak local pressures (i.e., 2-4 times normal or more, sometimes over 5.0 MPa) are loosely associated with cartilage deterioration over time. Evidence as well as intuition suggests contact stresses per se are not associated with deterioration, although some associated quantity (e.g., stress gradient) over time might be. Therefore, we may not presume that contact stresses, whether peak or spatially averaged provide a good surrogate for biological behavior. Rather, spatial and temporal aspects of the loading history induce the biological responses.

Finally, let me make an observation about "weight-bearing joints." Many authors imply that those joints involved directly in gait (i.e., the lower extremity joints in bipedal animals) somehow experience greater loads and stresses. While it might be true the loads are higher, the joints are also much larger. The available evidence I have reviewed suggests the contact stresses (if not stress histories) are similar in all joints. Thus, it is appealing to speculate joints have evolved to some aspect of contact stresses or stress histories, not loads. That being the case, the concept of a "weight-bearing joint" is misleading and perhaps the term should be abandoned.

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